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[2+2]-Photocycloaddition Reactions in the Synthesis of Novel Scaffolds and Natural Products

[2+2]-Photocycloaddition Reactions in the Synthesis of Novel Scaffolds and Natural Products

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A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Science.

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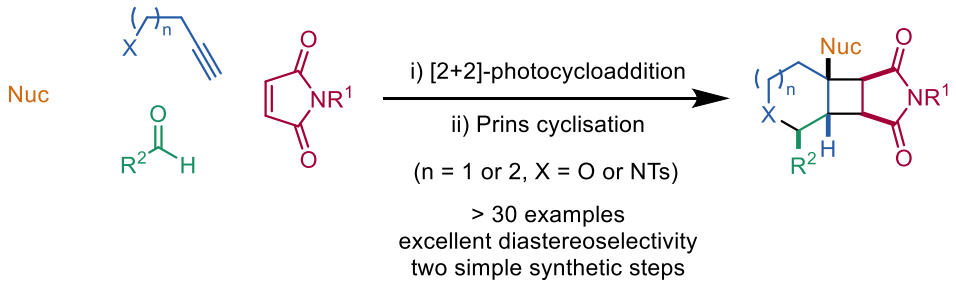
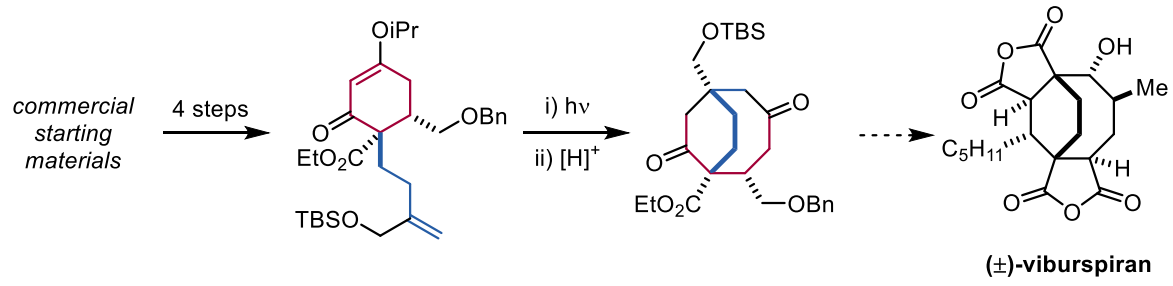
Abstract

[2+2]-Photocycloaddition reactions are a valuable method for the synthesis of cyclobutanes and cyclobutenes, as the basis for complex novel ring-systems, or as intermediates in the synthesis of natural products. This thesis outlines the use of such cycloaddition reactions in two distinct applications; the synthesis of novel tricyclic scaffolds; and a route towards the maleidride natural product, viburspiran. An introduction to photochemistry is given in Chapter 1, followed by specific details pertaining to [2+2]-cycloaddition reactions.

In Chapter 2, a method for the synthesis of fused cyclobutane heterocycles using tandem [2+2]-photocycloaddition and Prins cyclisation reactions is outlined. This modular method allows the transformation of four simple starting materials into complex tricyclic systems. The two-step process offers excellent diastereoselectivity and the products formed contain multiple points for further derivatisation, making them attractive novel scaffolds for drug-like libraries in medicinal chemistry.



Chapter 3 describes the use of [2+2]-cycloadditions for the total synthesis of the core carbocyclic scaffold of maleidride natural product viburspiran. The proposed key step involves an intramolecular de Mayo reaction which upon ring opening, allows synthesis of the bridged cyclooctane structure of viburspiran. A strategy for the completion of the total synthesis has been devised and is currently under investigation.



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Finally, thank-you to my family, especially to my parents for your complete and unwavering love, support and encouragement in everything I do.

(Some glassware was harmed in the making of this thesis.)

Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: ..... DATE:.....

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
ADEQUATE	adequate double quantum transfer experiment
aq.	aqueous
C	Celsius
CD	circular dichroism
COSY	^{1}H-^{1}H correlation spectroscopy
DCM	dichloromethane
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DIAD	diisopropylazodicarboxylate
DMAP	dimethylaminopyridine
DMC	dimethylcarbonate
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*-*N*'-dimethylpropyleneurea
DMSO	dimethylsulfoxide
DOE	Design of Experiments
dr	diastereomeric ratio
EDG	electron donating group
EE	ethoxyethyl acetal
ee	enantiomeric excess
equiv.	equivalents
er	enantiomeric ratio
ESI	electrospray ionisation
EWG	electron withdrawing group
g	grams
GABA	gamma-aminobutyric acid
h	hours
HMBC	heteronuclear multiple bond correlation
HMDS	bis(trimethylsilyl)amine
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
hrPKS	highly reducing polyketide synthase
HSQC	heteronuclear single quantum coherence
Hz	Hertz
IC	internal conversion
im	imidazole
INADEQUATE	incredible natural abundance double quantum transfer experiment
IR	infrared
IRD	inter-radical distance
ISC	inter-system crossing

ITX	isopropylthioxanthone
LDA	lithium diisopropylamide
LHS	left-hand side
LUMO	lowest unoccupied molecular orbital
M	molar
m.p.	melting point
m/z	mass:charge ratio
M^+	molecular ion
min	minutes
MO	molecular orbital
mol	moles (unit)
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
no.	number
NOE	nuclear Overhauser effect
Nu	nucleophile
OVAT	one-variable-at-a-time
PES	potential energy surface
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
ppm	parts per million
*p*TSA	*para*-toluenesulfonic acid
quant.	quantitative
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
RHS	right-hand side
rt	room temperature
S_n	singlet state
SOMO	singly occupied molecular orbital
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBME	*tert*-butylmethyl ether
TBS	*tert*-butyldimethylsilyl
TCNB	1,2,4,5-tetrachloro-3-nitrobenzene
temp.	temperature
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMS	trimethylsilyl
T_n	triplet state
UHPLC	ultra high-performance liquid chromatography
UV	ultraviolet

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Chapter 1: Introduction

1. Introduction

1.1. History of Photochemistry

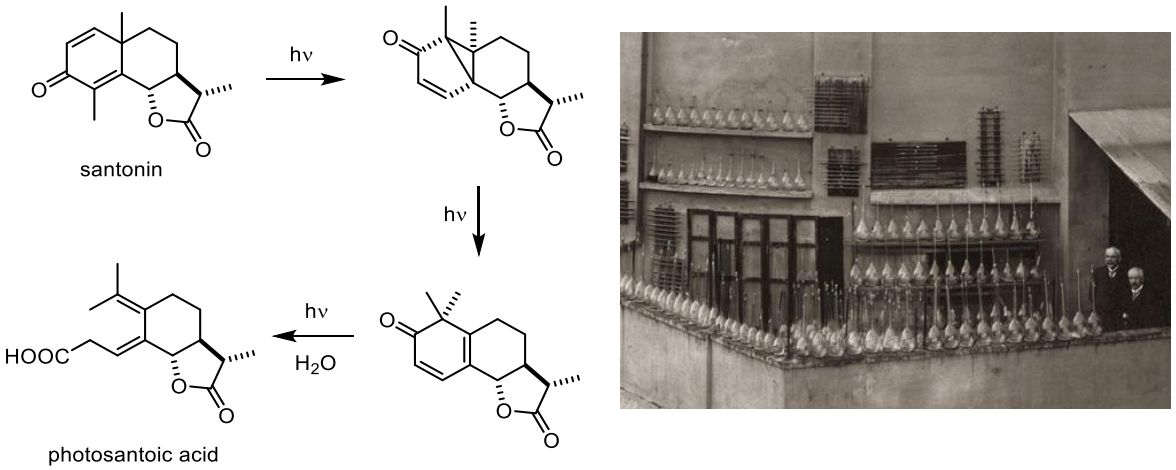
In the early 1900s Italian photochemist Giacomo Luigi Ciamician became one of the first scientists to outline the increasing need for an effective replacement for fossil fuels. 'The Photochemistry of the Future' was published in 1912, describing how photochemical reactions, achieved so easily by plants, should be the inspiration for the much-needed change in energy sourcing.[1] As well as suggesting that solar energy should be a future alternative to fossil fuels, Ciamician also highlighted the importance of photochemistry as a method for the synthesis of complex molecules. On the photochemical pathways active in plants, he wrote:

"Plants are unsurpassed masters of photochemical synthesis of the fundamental substances, building up from carbon dioxide with the help of solar energy. They also produce the so-called secondary substances with the greatest ease." – Ciamician[1]

As well as his pioneering work in this field of artificial photosynthesis, in his earlier work Ciamician was one of the first chemists to discover the link between colour and molecular structure. This discovery was one of the first insights into how molecules absorb light and the properties that result from their absorption. This was followed in 1876 by Witt *et al.* who more formally coined the term 'chromophore' to describe the specific region of a molecule that has the potential to create colour.[2]

Many years before these key observations were made, organic photochemical reactions had been observed and described; for example the photoreaction of santonin observed by Trommsdorff in 1834 (Scheme 1).[3] He observed that exposure to sunlight caused santonin to turn yellow, an observation which was later explained by Sestini and Cannizzaro as the formation of photosantonic acid, the structure of which was not fully realised until 1958.[4,5]

Early photochemical reactions used exclusively sunlight as a photon source, with only a handful of useful reactions identified. The development of mercury arc lamps at the turn of the twentieth century allowed more specific photochemical transformations to be performed by narrowing the spectrum of light that could be used.[6] These technological advances, along with developments in analytical techniques, have allowed the field of organic photochemistry to expand to become a prominent research area within organic chemistry. Many established photochemical reactions have been applied in the synthesis of natural products and highly complex novel scaffolds.[7]



Scheme 1 – Formation of photosantonic acid from santonin[3] (left) and Ciamician's sun-exposed laboratory balcony in Bologna (right)

1.2. Theoretical Photochemistry

Photochemistry is the study of the interaction of light with molecules. Generally, this involves a molecule absorbing radiation in the ultraviolet, visible, or infrared region of the electromagnetic spectrum, allowing it to undergo a chemical transformation. Reactions involving photochemical activation proceed via high energy intermediates that often cannot be generated thermally. This allows molecules to overcome activation barriers for reactions and undergo transformations that are not possible with ground state chemistry.

Wave-particle duality is a quantum mechanical concept that describes how light exhibits both wave and particle like behaviour. As a particle, light can be described as discrete packages called photons, that have a quantised energy levels depending on their wavelength. Molecules have various quantised translational, rotational, vibrational and electronic energy levels. Thermal energy allows excitation of translational, rotational and vibration states, however electronic excited states require vast amounts of heat to become thermally accessible. The use of ultraviolet light allows electronic excited states to become accessible under ambient conditions.

There are two main laws that govern the theory of photochemical reactions. The Grotthuss–Draper Law (1812)[2] states that for a photochemical reaction to take place, the molecule must absorb a photon of light. This is extended by the Stark–Einstein law (1908-1913)[2] which specifies that for each photon absorbed by the system, one molecule is activated for the given photochemical reaction. The efficiency of a photochemical reaction can therefore be quantified by its quantum yield; the amount of product formed per unit of photons absorbed.[8] Typically quantum yield values for photochemical processes are less than 1 as not all photons absorbed lead to productive outcomes.

When a ground state singlet (S_0) molecule absorbs light of required energy, an electron can be promoted to a higher singlet energy orbital (S_1) (Figure 1). Upon this excitation from HOMO (highest occupied molecular orbital) to LUMO (lowest unoccupied molecular orbital), the spin of the electron is conserved due to the law of conservation of angular momentum. Following this initial excitation, several processes can occur. Higher energy singlet excited states can be accessed (S_2, S_3 etc.), however Kasha's rule states that photon emission can only occur from the lowest excited state of a given multiplicity.[2] This means that higher energy states are short-lived and often relax back to S_1 quickly through processes such as internal conversion (IC). Excited singlet states (e.g. S_1) can undergo inter-system crossing (ISC) to access the excited triplet state T_1 where both electrons have the same spin; this is a lower energy state. Radiative relaxation pathways to S_0 can occur either from S_1 (fluorescence) or T_1 (phosphorescence). Both S_1 and T_1 states have low energy half-full orbitals and are therefore more reactive than the ground state. The processes described above are summarised in a Jablonski diagram (Figure 1).[2]

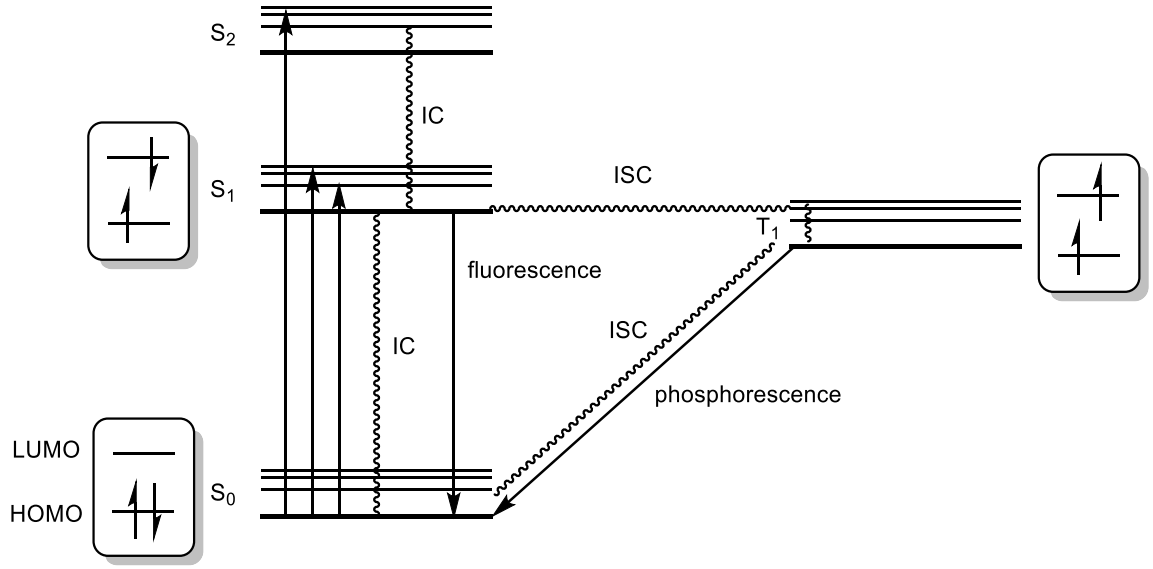


Figure 1 – Jablonski diagram showing energy levels and transitions in photochemical reactions[2]

Excited state molecules differ dramatically in their reactivity from ground state molecules, a property which is exploited in organic photochemistry. The efficiency of photochemical reactions is limited by the lifetime of the excited state.[2]

In some cases, when the reactant molecule undergoes inefficient ISC from singlet to triplet states, the use of photosensitising molecules such as acetone, benzophenone or acetophenone is necessary. Photosensitisers are molecules that can be selectively excited to T_1 to then transfer energy to the reacting molecule. Efficient photosensitisers have a triplet state energy greater than that of the reacting molecule.[7,9]

1.3. Practical Photochemistry

There are several practical considerations to be made when setting up a photochemical reaction. Glassware must be suitable for the reaction is it used for, as some glasses absorb certain wavelengths of UV light, preventing it from reaching the reaction. Pyrex for example absorbs light with wavelengths shorter than ~275 nm, so quartz reaction vessels are often used for reactions that require shorter wavelengths as they allow all light with wavelengths above 170 nm to pass through. Mercury arc lamps are the most commonly used source of UV light, with the spectra of light produced dependent on the mercury vapour pressure. Low pressure lamps emit primarily light of wavelengths 253.7 and 184.9 nm, while in medium pressure lamps, where mercury atoms undergo more frequent collisions with electrons, wavelengths of 313.9 and 365.4 nm are accessible (Figure 2). Mercury arc lamps often require water cooling due to high running temperatures that can reach up to around 600 °C.[10]

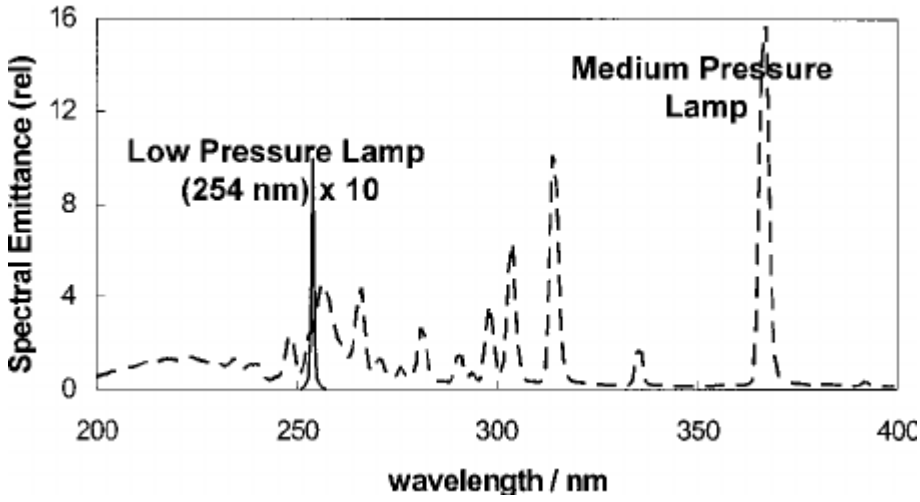


Figure 2 – Wavelengths of light emitted by low and medium pressure mercury-arc lamps[10]

1.4. Organic Photochemistry

In organic molecules, the nature of the chromophore dictates the wavelengths of light that can be absorbed. In most cases chromophores are predominantly made up of conjugated π-bonds and lone pairs on heteroatoms, resulting in transitions between bonding and anti-bonding orbitals upon absorption of a photon of light. Inner shell electrons are not involved in photochemical excitation and so only valence electrons are considered. The transitions most commonly observed in organic molecules, shown in Figure 3, are mainly low energy n-π* or π-π* transitions; σ-σ* transitions are much higher in energy and are rarely observed in organic photochemistry.

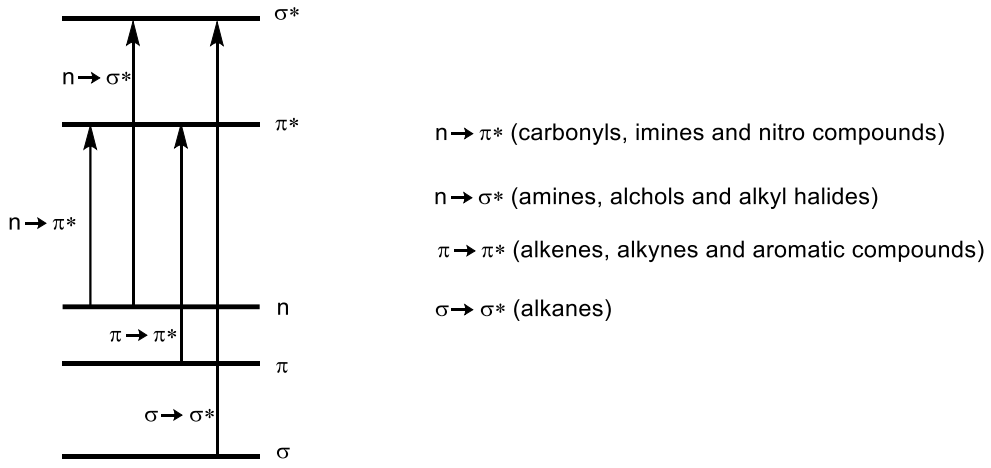


Figure 3 – Typical transitions in organic photochemistry

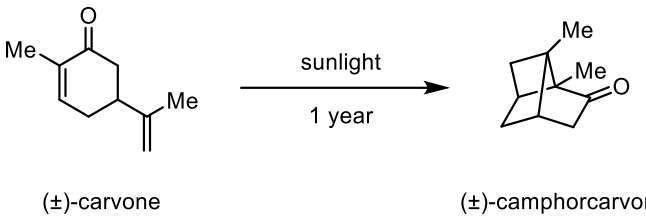
UV-visible absorption spectroscopy is a valuable tool in predicting the reactivity of an organic molecule towards ultraviolet light, providing information about the wavelengths absorbed by a molecule. However, UV-visible spectroscopy does not provide any information about subsequent photophysical processes such as IC. Table 1 describes some characteristic absorbances for isolated functional groups, which can be useful in predicting reactivity, however these values do not take into account additional conjugation or the wider chromophore. These values were calculated based on theoretical data from single molecules and monochromatic light.[11]

Table 1 – Common chromophores and their absorbance[11]

chromophore	transition	λ_{max} /nm	chromophore	transition	λ_{max} /nm
N=O	n → π*	660	C=N	n → π*	240
C=S	n → π*	520	C=C-C=O	π → π*	220
N=N	n → π*	350	C=C-C=C	π → π*	220
C=C-C=O	n → π*	350	S=O	n → π*	210
C=O	n → π*	280	C=C	π → π*	180
C_6H_6	π → π*	260	C-C, C-H	σ → σ*	< 180

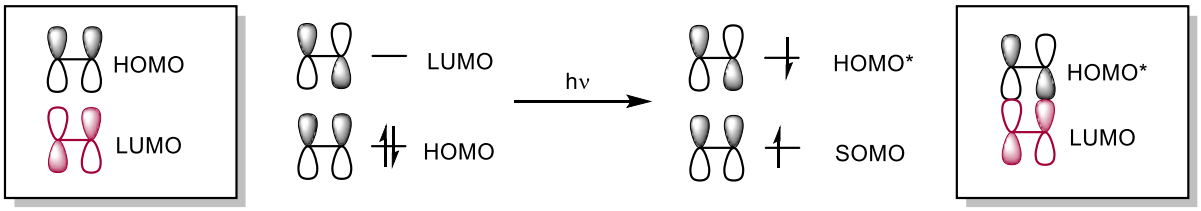
1.4.1. [2+2]-Photocycloaddition

[2+2]-Photocycloadditions are arguably one of the most commonly used and studied photochemical reactions.[12] The first example was reported in 1908 by Ciamician who observed that carvone had undergone a photochemical reaction after being left exposed to light for up to a year (Scheme 2).[13] It was not until 1957 that the proposed structure of the product of this [2+2]-photocycloaddition was confirmed by Büchi and Goldman.[14] Following extensive investigations into the mechanistic aspects of this reaction, it has been utilised in numerous total syntheses, as well as in the synthesis of interesting non-natural compounds such as cubane.[7,15,16]



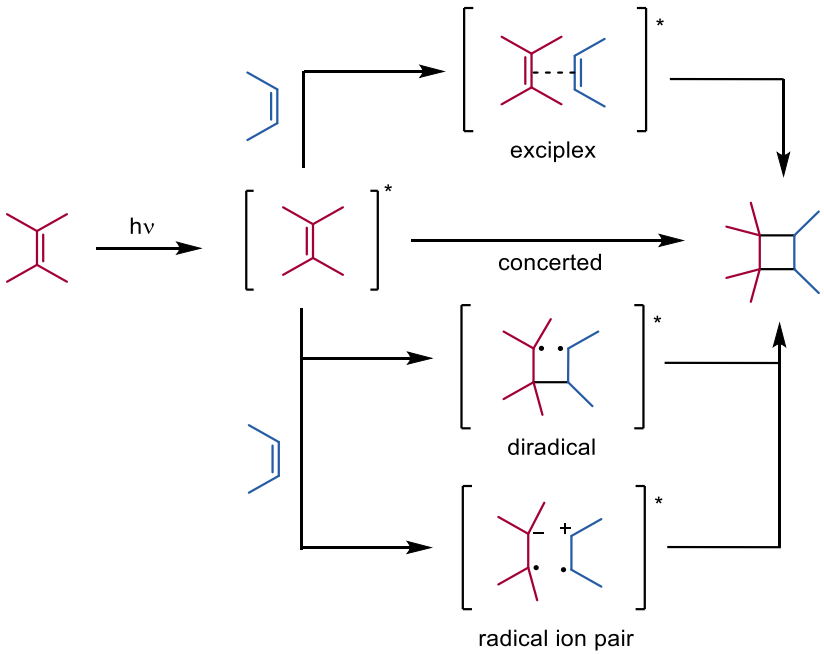
Scheme 2 – [2+2]-Photocycloaddition of carvone to form camphorcarvone[13]

For cycloaddition reactions to take place, the orbitals in each π-system must form a favourable interaction. Thermally, the HOMO and LUMO of two alkenes are not of the right phase to successfully overlap, however upon photochemical excitation, an electron can be excited from the HOMO to form a new singly occupied HOMO* and a SOMO (singly occupied molecular orbital) as shown in Scheme 3. Overlap between the HOMO* and LUMO of a ground state molecule allows the [2+2]-photocycloaddition to proceed. Enones are often used as one of the components in [2+2]-cycloadditions, as additional conjugation leads to a smaller HOMO-LUMO gap, and therefore more effective excitation.



Scheme 3 – Orbital considerations in [2+2]-photocycloadditions

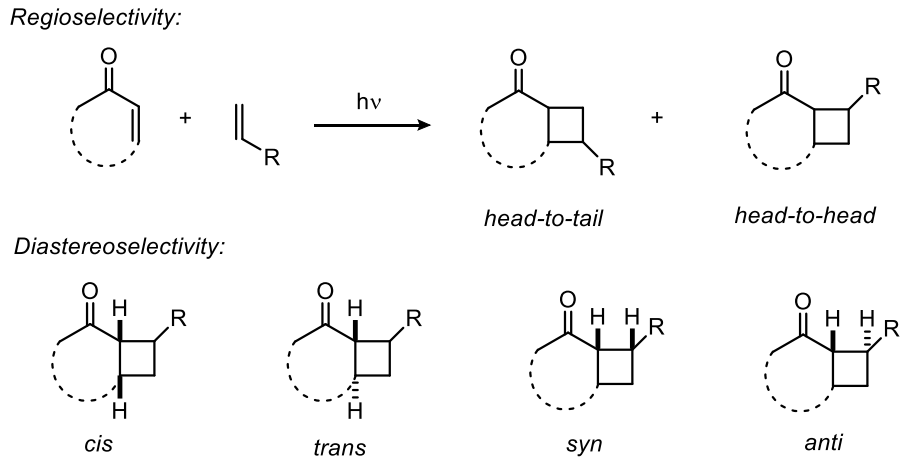
For [2+2]-photocycloaddition, the possible mechanistic pathways have been extensively investigated but ultimately depend on the conditions and substrate. One component in the reaction, usually an enone or other functional group able to act as a chromophore, undergoes photoexcitation to an S_n state. Often this singlet state is short-lived, due to its ability to decay through ISC to a T_n state, and can then form an excited complex (exciplex) with the other component in the reaction in its ground state, usually an alkene, thus forming triplet diradical (Scheme 4). The final bond can then be formed following internal conversion to the singlet diradical. Reactions going through the concerted pathway will generally be stereospecific, whilst due to possible bond rotations, other mechanisms result in loss of specificity.[17]



Scheme 4 – Possible mechanisms for [2+2]-photocycloadditions

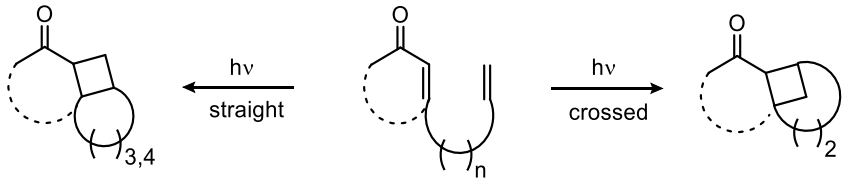
Another factor to consider which has been the subject of extensive theoretical study, is the regioselectivity in [2+2]-cycloadditions.[18,19] In most cases, the reacting alkenes are not symmetrical and the regioselectivity of addition can give various products. For [2+2]-reactions between enones and alkenes, alkenes with an electron donating group such as a methoxy (R = OMe) usually give the head-to-tail product, whereas electron withdrawing groups such as nitrile (R = CN) give the head-to-head product as shown in Scheme 5.[20] Although this general rule can be used in most cases, there are exceptions, and the effect is less pronounced with electron withdrawing substituents.[21,22] Other variables such as solvent, temperature and steric interactions can influence the regiochemical outcome.[9]

As well as regioselectivity, diastereoselectivity must be considered. Up to four new stereocentres can be created through [2+2]-cycloaddition, allowing in some cases up to 16 possible stereoisomers to form, although often the system will be biased towards several major isomers. For cyclobutane bonds annulated to another ring, the relationship along the bond is described as *cis* or *trans*, and for bonds not annulated to another ring, the relationship can be described as *syn* or *anti* (Scheme 5).[9] In some cases, the stereochemical outcome of [2+2]-cycloadditions can be influenced by stereochemistry in the starting material. Most stereocontrolled [2+2]-cycloadditions rely on intramolecular additions to control the orientation of the approaching alkene.[23,24]



Scheme 5 – Regioselectivity and diastereoselectivity in [2+2]-photocycloaddition of enones[9]

Regiochemical outcomes of intramolecular [2+2]-cycloadditions have frequently been explained using the 'rule of five';[25] a term used to describe the preferential formation of 5-membered rings in photochemical [2+2]-reactions. It is analogous to the observations by Beckwith who reported that the ring closure of hex-5-enyl radicals proceed to give the cyclopentyl product 75 times faster than the cyclohexyl product.[26] A similar observation was made in photochemical processes in 1967 by both Srinivasan and Hammond.[27,28] This was investigated further by Maradyn and Weedon through experiments that investigated trapping the biradical intermediates using hydrogen selenide.[29] Of four possible biradicals, the only two that progressed to form products were those that led to 5-membered rings, indicating that any other biradical intermediates formed must fragment to starting material. For enones with tethered alkenes, two regioisomeric products are possible and for a tether length of 3 (or 4) the straight product gives a more favourable 5-membered ring (Scheme 6, left). For a 2-carbon tether length, the crossed product dominates (Scheme 6, right), preventing the formation of an additional 4-membered ring due to the additional energy associated with strained rings.[27,28]

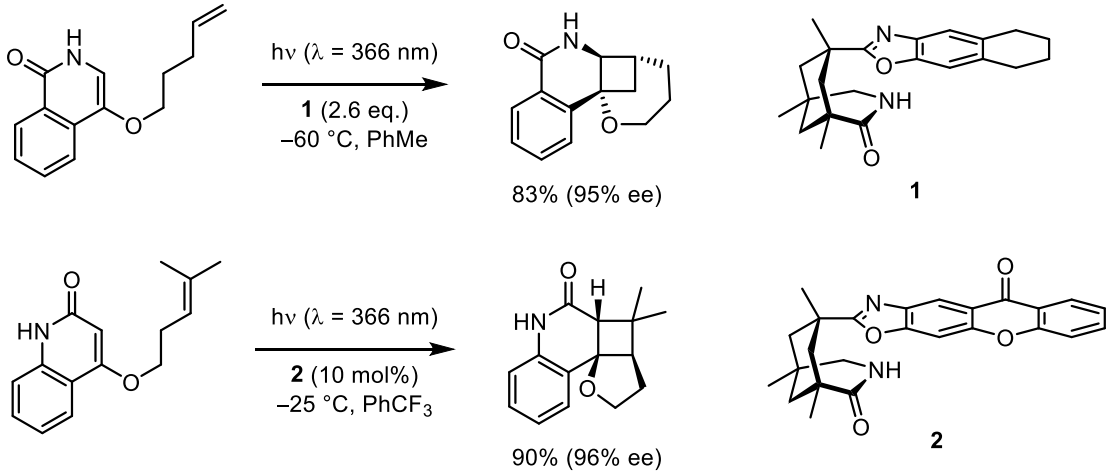


Scheme 6 - Regioselectivity for the intramolecular [2+2]-photocycloaddition of enones[9]

Although a good method for the prediction of regiochemistry in these reactions, the 'rule of five' does not correctly predict the results in all cases, for example enones in which a tether is not attached to the α- or β-carbon of the enone.[30] As an alternative method for the prediction of regiochemical outcome, computational calculations of the biradical intermediates have been previously shown to be successful.[30,31] Calculation of the minimum energy conformations of all

possible biradical intermediates can explain the regiochemistry for those examples that do not fit the 'rule of five' explanation, as well as confirming those that do. A suitable conformation for ring closure has been considered one with a short inter-radical distance (IRD) of approximately 3 Å.

Enantioselective photochemical reactions are particularly challenging and efforts in this area have only recently come to fruition. Reactions initiated by UV/visible light cannot induce significant asymmetric induction, even if the light used is in a circularly polarised form.[32,33] More successful methods have included induction of asymmetry through chiral substituents, complexing agent, photosensitisers or solvents. Bach *et al.* have reported the use of chiral lactam complexing agents **1** that induce facial discrimination and therefore allows both intra- and intermolecular [2+2]-cycloadditions to be conducted enantioselectively (Scheme 7).[34–36] Later developments to the chiral template led to the thioxanthone **2** which as well as a chiral template also acts as a photosensitiser and allows similar transformations to be carried out catalytically.[37]



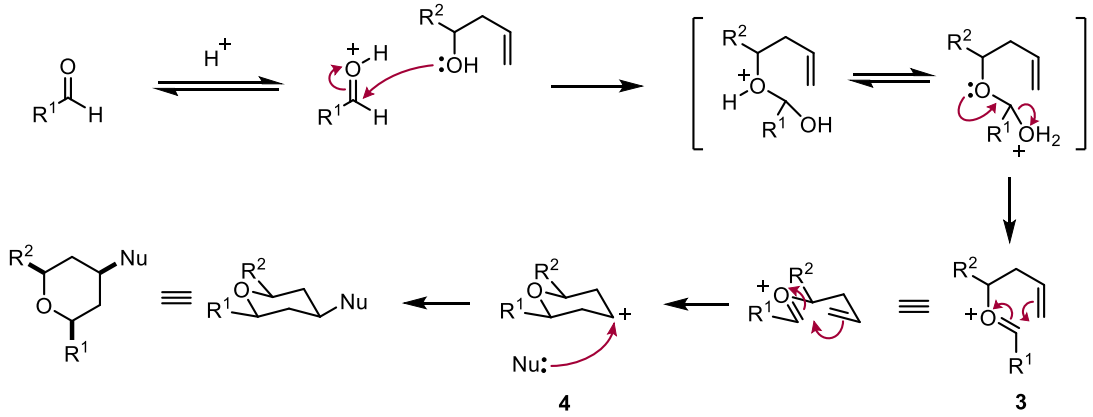
Scheme 7 – Use of chiral templates for enantioselective [2+2]-photocycloaddition reactions[34–36]

Chapter 2: Prins Cyclisation of Photochemically Synthesised Cyclobutenes

2. Prins Cyclisation of Photochemically Synthesised Cyclobutenes

2.1. Introduction to the Prins Cyclisation

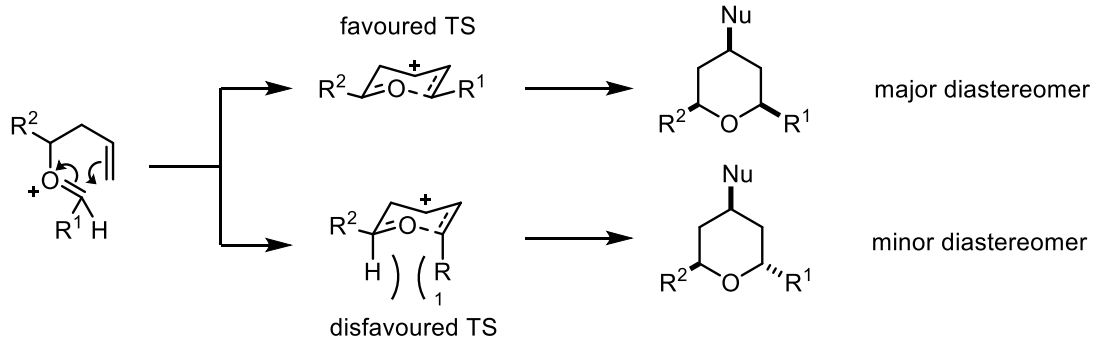
The Prins cyclisation involves formation of an oxocarbenium ion, for example through the acid-mediated reaction of a homoallylic alcohol with an aldehyde, to synthesise tetrahydropyran rings. Hendrik Jacobus Prins discovered the reaction during his doctoral studies in 1919.[38] It has now become a powerful method for the formation of C-C and C-O bonds, as well as being successful to reliably create stereocentres around a tetrahydropyran ring. The reaction and its applications have been widely reviewed so only a concise introduction to Prins cyclisations is given here.[39–42]



Scheme 8 – Mechanism of the Prins cyclisation

The mechanism of the reaction begins with protonation of an aldehyde or coordination of a Lewis acid (Scheme 8). This facilitates attack of the alcohol onto the aldehyde, followed by loss of water to form an oxocarbenium ion **3**. Cyclisation via a chair transition state then forms carbocation **4** with the conformation of the transition state setting the stereochemistry of the groups positioned around the ring. The final step involves the attack of the carbocation by an appropriate nucleophile.

The stereochemical control can be attributed to the nature of the transition states in this reaction. During the cyclisation step, the attack can proceed to give one of two possible chair conformations (Scheme 9). The favoured transition state is the one in which substituents are oriented equatorially, to minimise unfavourable 1,3-diaxial interactions. Attack from the nucleophile also occurs to give the most stable chair conformation.



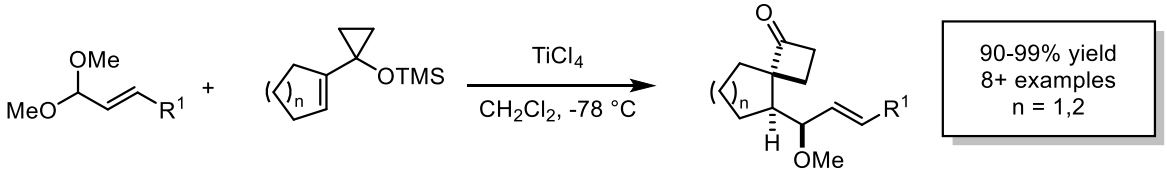
Scheme 9 – Stereochemical control in the Prins cyclisation

As well as its desirable diastereoselectivity, the reaction is also versatile and a wide range of reaction conditions have been identified, including the use of olefins with differing substitution patterns, various nucleophiles, and substituted aldehydes. Variations on the reaction have also been investigated widely, including the aza-Prins reaction,[43] tandem processes such as the Prins-pinacol[44] and Prins-Friedel-Crafts[45] reactions, and reductive[46] and oxidative[47] Prins cyclisation reactions.

2.1.1. Prins Reactions for the Synthesis of Fused Ring Systems

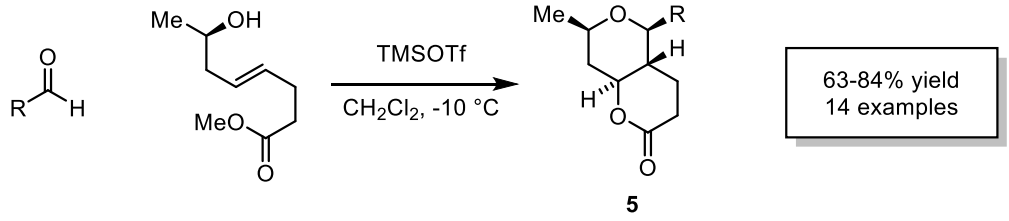
As a carbon-carbon bond forming reaction, the Prins cyclisation is an important transformation in synthetic organic chemistry and has been utilised in the formation of many different tetrahydropyrans. It has been employed for the synthesis of five, seven, eight and nine membered rings and aza-cyclisations have also been developed.[48–50] Despite this, the scope of the cyclisation with respect to the alkene component has been limited, with most cases involving only terminal or 1,2-disubstituted alkenes.[41] Examples of Prins cyclisations which contain the alkene within a ring system itself are rare, but the few examples reported have provided facile access to novel core structures.

One such example was reported in 2007 by Cha *et al.* in which addition of TMS ethers to α,β-unsaturated acetals under acidic conditions was shown to give spirocyclobutanones with the formation of three contiguous stereocentres (Scheme 10).[51] The reaction is diastereoselective and has been shown to work with both cyclopentene and cyclohexenes. It has also been used in the total synthesis of natural products cyathin A_3 and cyathin B_2,[52] and lepadiformines A and C.[53]



Scheme 10 – Prins-type reaction of cycloalkenylcyclopropanol silyl ethers and α,β-unsaturated aldehyde acetals[51]

One of the first general examples of the use of Prins cyclisations for the formation of a fused bicyclic system was published by Willis *et al.* in 2008. In this reaction the homoallylic alcohol has a tethered nucleophile, in this case a methyl ester, that can be used to intramolecularly trap the carbocation intermediate, giving the novel bicyclic products of the general structure **5** in good yields and with the generation of three new stereogenic centres (Scheme 11).[54]



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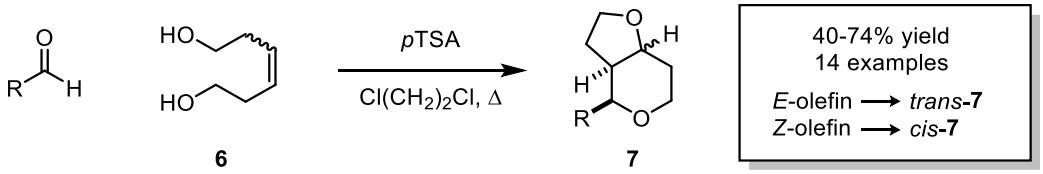
Scheme 11 – Prins cyclisation for the synthesis of bicyclic tetrahydropyrans using an internal nucleophile[54]

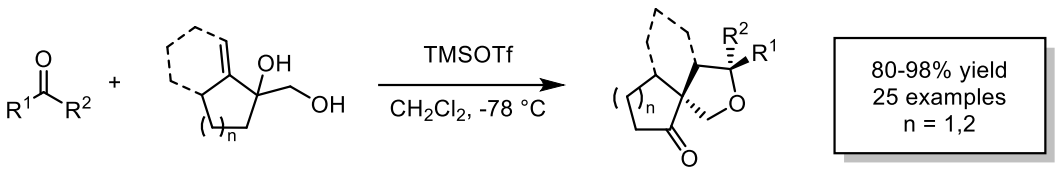
Following on from this work, alcohols were also shown to be successful nucleophiles in intramolecular Prins cyclisations in 2009 by Yadav *et al.* (Scheme 12).[55] Using *E*- or *Z*-olefins in the cyclisation of diol **6** with a range of aldehydes gave the *trans* and *cis*-bicyclic products **7** respectively in good yields.



6 **7**

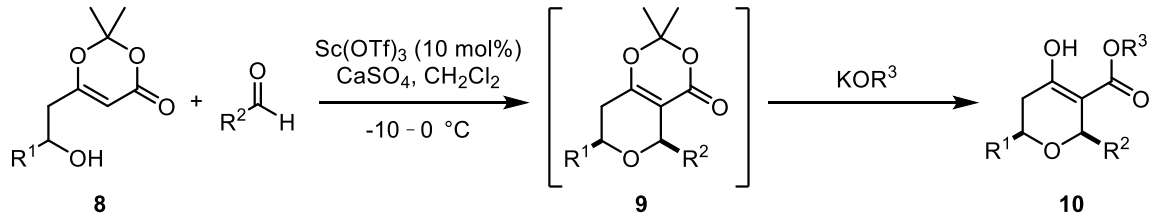
Scheme 12 – Use of alcohols as nucleophiles in intramolecular Prins cyclisations[55]

A further interesting example of the use of cyclic alkenes in Prins cyclisation was reported in 2009 by Chavre *et al.* in which oxaspirocycles were synthesised in good yields and diastereoselectivity through reaction of cycloalkene diols (Scheme 13).[56]



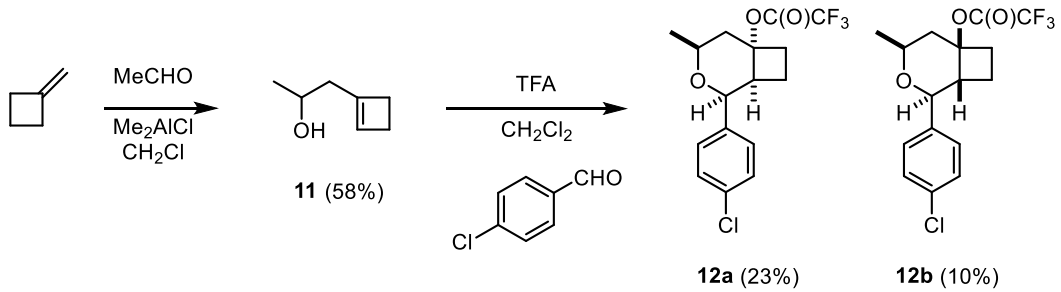
Scheme 13 – Synthesis of oxaspirobicycles by the Prins cyclisation of cyclic alkene diols[56]

One of the most commonly reported examples of Prins cyclisations using alternative alkene components is the use of dioxenones. First reported in 2005 by Scheidt *et al.* this reaction takes the readily formed dioxenone alcohols **8** and in a reaction with aldehydes under acidic conditions forms the highly substituted dihydropyrans **9** in good yields and diastereoselectivity (Scheme 14).[57] The dioxenones were deprotected under basic conditions to give the β-keto ester **10** products. This work was later extended to allow the preparation of spirooxindole pyrans[58] and more recently a similar reaction involving a tandem oxidative cleavage/Prins cyclisation to synthesise oxa-bridged carbocyclic rings has been reported.[59]



Scheme 14 – Prins cyclisations of substituted dioxenones to give tetrahydropyran-4-ones[57]

Although the Prins reaction has been applied to cyclic alkenes, cyclobutenes have rarely been used in Prins cyclisations. To the best of our knowledge, the only published example was carried out in the Willis research group where the simple cyclobutene **11** was reacted with *p*-chlorobenzaldehyde in the presence of TFA to give tetrahydropyrans **12a** and **12b**, albeit in low yield and as a mixture of diastereomers (Scheme 15).[60] This offers a powerful tool for the synthesis of fused [4.2.0]-oxabicycles and warrants further investigations. Photochemistry allows straightforward access to the necessary cyclobutene starting materials.



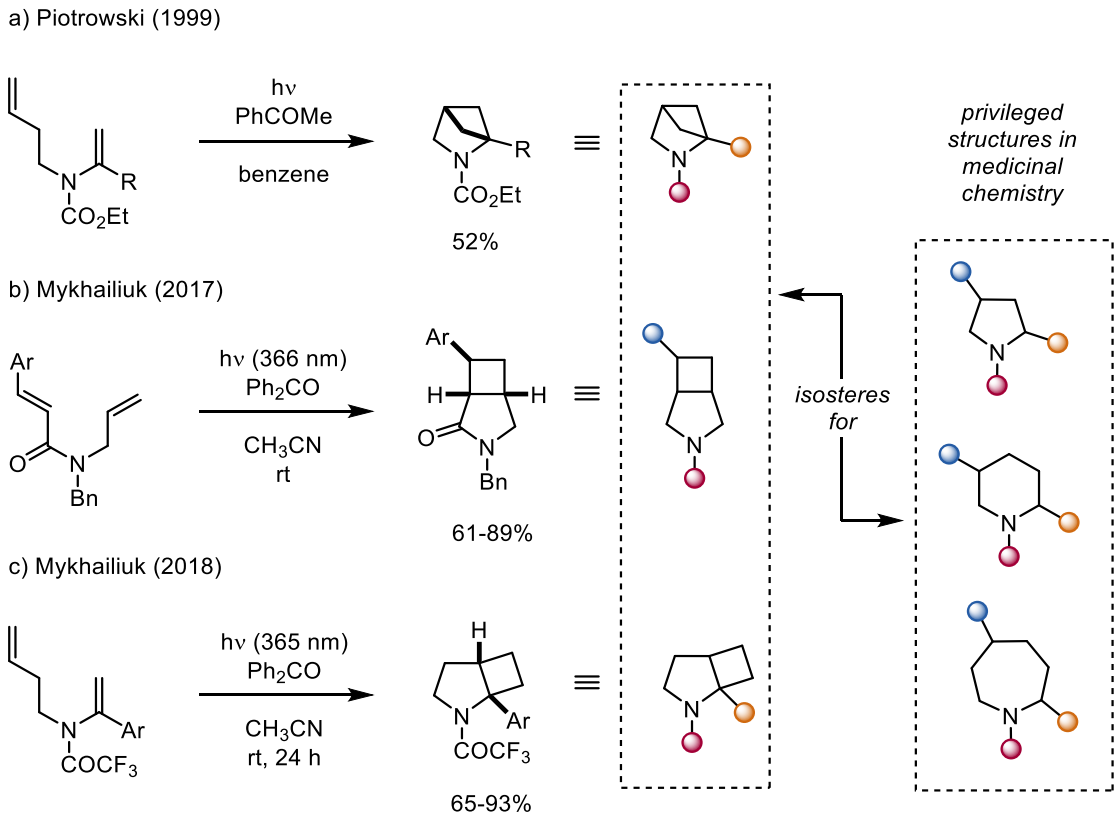
Scheme 15 – Prins cyclisation with cyclobutene **11** by G. Parker[60]

2.1.2. Scaffolds in Medicinal Chemistry

Although the development of methods for forming sp^2-sp^2 bonds has been extremely successful in recent years, the range of structures that can be synthesised through these approaches are limited, and there is a demand from the drug-development industry for methods to synthesise sp^3-rich molecules.[61–63] The seminal publication *'Escape from Flatland'* describes this problem and outlines the success of drug compounds with a high Fsp^3 values, (number of sp^3 hybridised carbons/total carbon count).[64,65]

Also valuable to medicinal chemistry is the ability to derivatise core structures to produce structurally related compounds. An investigation published in 2014 on the structural diversity of nitrogen containing pharmaceuticals described the frequency with which identical core structures are found in successful pharmaceuticals.[66] This analysis also found that 59% of small-molecule drugs contain a nitrogen heterocycle, with piperidine, piperazine and pyrrolidine among the most common aliphatic examples. Development of methods for the synthesis of these common saturated nitrogen heterocycles is therefore of clear industrial importance.[67]

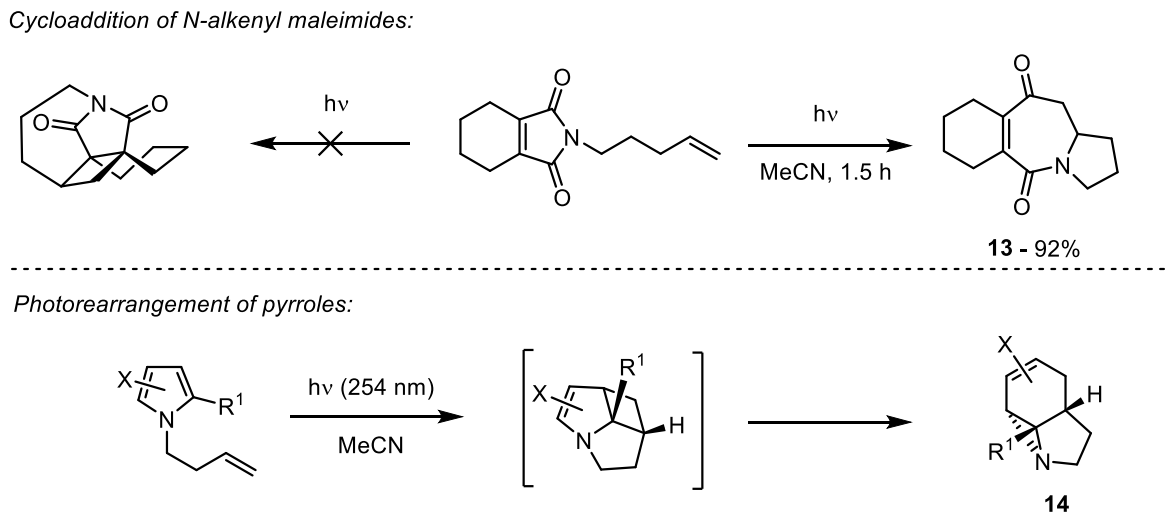
One drawback of the use of saturated heterocycles in drug development is the lack of structural rigidity they confer. Use of saturated bicycles or bridged systems can be one way to add conformational restriction to the scaffold that can mimic the rigidity of unsaturated systems without compromising the added benefit of three-dimensionality. Research in this area has recently proposed the use of nitrogen bicycles as analogues for piperidine, morpholine, piperazine and GABA.[68,69] Synthesis of these scaffolds can be achieved photochemically and the resulting products can be easily functionalised at multiple positions to act as analogues for the monocyclic systems (Scheme 16a-c).[69–71]



Scheme 16 – Synthesis of conformationally restricted bicyclic isosteres using [2+2]-photocycloaddition[69–71]

Photochemical methods are ideal for the formation of conformationally restricted cyclobutanes and the Booker-Milburn group has previously had success in this area, for example the intramolecular photocycloaddition of *N*-alkenyl substituted maleimides to construct ring expanded amides **13**,[72] or the synthesis of tricyclic aziridines **14** from a photochemical pyrrole rearrangement (Scheme 17).[73] Both reactions generate complex polyheterocycles with a high proportion of sp^3 centres, demonstrating the utility of photochemistry for novel scaffold synthesis. Research in our group has also focussed on the scale-up of such reactions, to make them synthetically valuable in an industrial setting. In order to do this, new reactors for flow photochemistry have been developed, allowing the synthesis of large quantities of photochemical products.[74,75] Many of these molecules also include groups that could be further

functionalised either for their use as scaffolds in drug libraries, or for the creation of further complex core structures.



Scheme 17 – Photochemical synthesis of small complex molecules by the Booker–Milburn group[72,73]

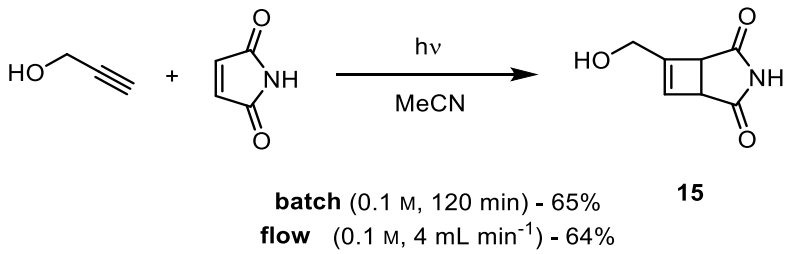
2.1.3. Cyclobutene Synthesis

Cyclobutanes and cyclobutenes are versatile structures in organic chemistry due to their inherent ring strain. Relief of ring strain provides a driving force for further synthetic transformations such as ring opening to acyclic products or ring expansion. Despite their synthetic utility approaches for their synthesis are dominated by photochemical [2+2]-cycloaddition reactions. Other methods that have been less frequently used for the preparation of cyclobutanes and cyclobutenes include ring expansions of cyclopropyl precursors, ring contractions and 1,4-cyclisation of acyclic precursors.[9,76,77]

[2+2]-Photocycloaddition of chromophores with alkenes is arguably one of the most useful photochemical processes in synthesis allowing a relatively facile and tuneable method for the synthesis of cyclobutanes and cyclobutenes. In the Booker-Milburn group, extensive research has been carried out specifically on the [2+2]-photocycloaddition of maleimides with various alkynes and alkenes. Maleimides are excellent chromophores with a strong absorption in the UV region at ~275 nm.[78] Cycloaddition reactions using maleimides as the chromophore have been used routinely as a method for accessing functionalised cyclobutanes as they offer flexibility in the possible derivatives afforded from reduction of the resulting succinimide.

The cycloaddition of maleimide with propargyl alcohol to form cyclobutene **15**, has been used as a model photochemical reaction to determine the advantages of flow chemistry over batch (Scheme 18).[78] Reaction yields were around 65% in both batch and flow, with the productivity slightly higher for flow, and in most cases, it was found that yields for batch and flow reactions were essentially the same at full conversion. As reactions can be successfully

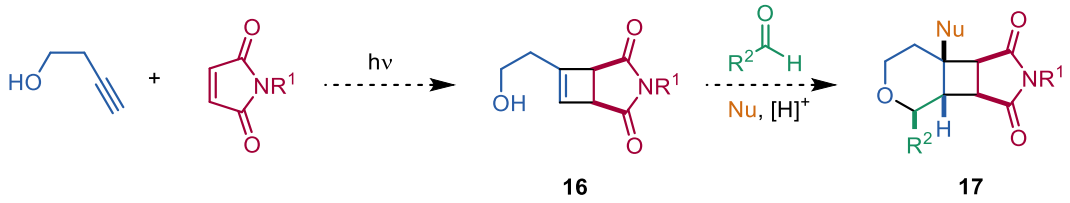
scaled up using our flow reactors, the choice of batch or flow can be informed by other aspects of the reaction.



Scheme 18 – Synthesis of succinimide-fused cyclobutene **15**; comparison of batch and flow methods[78]

2.2. Aims

Use of flow photochemistry allows access to large quantities of cyclobutenes using mild methods. The aim of this project was to combine the utility of flow photochemistry to access large quantities of cyclobutenes for use in Prins cyclisations, to provide a library of novel heterocycles. The products from the Prins cyclisation should have multiple sites for further functionalisation to make them amenable to medicinal chemistry, along with being synthesised in a diastereoselective fashion.



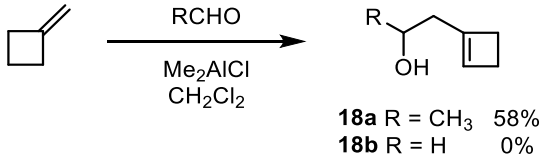
Scheme 19 – Proposed photochemical and Prins reactions for the synthesis of tricyclic structures **17**

It was proposed that cyclobutene alcohol **16** formed from reaction of maleimide with homopropargyl alcohol would be a suitable substrate for Prins cyclisation. This would allow formation of a further fused ring and give tricyclic products with the general structure **17**. The modular nature of the reaction allows multiple sites for further derivatisation for example by using different chromophores and substituted alkynes in the initial photochemical reaction, and by using various aldehydes and nucleophiles in the Prins cyclisation reaction. The versatility of the Prins cyclisation and the array of successful reaction conditions that have been previously published offer broad scope for development in this work.

2.3. Results and Discussion

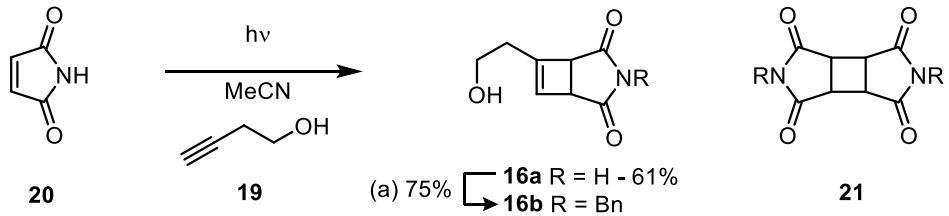
2.3.1. Substrate Synthesis

In previous unpublished work reported by Willis *et al.* on the Prins cyclisation of cyclobutenes, the homoallylic alcohol substrate was prepared through addition of methylenecyclobutane to acetaldehyde and Lewis acid dimethylaluminium chloride (Scheme 20) to give **18a**.[60] Unfortunately attempts to synthesise **18b** using the same method were unsuccessful, with volatility of the product a contributing factor. This problem highlights the benefits of photochemistry as a tool to access substituted cyclobutenes, providing both functionality that could be later derivatised along with an increase in molecular mass to aid isolation of the starting materials.



Scheme 20 – Attempt to synthesise cyclobutene alcohol **18b** for Prins reactions[60]

Due to the ease with which cyclobutenes can be synthesised through [2+2]-photocycloaddition reactions, homopropargyl alcohol **19** was reacted with maleimide **20** in acetonitrile to give cyclobutene alcohol **16a** as an appropriate substrate for the subsequent Prins reactions (Scheme 21). One minor drawback with the use of maleimide as a chromophore is its tendency to dimerise to form the by-product **21**. Much of the by-product can be removed by filtration of the reaction mixture prior to purification, however it was also found that formation of this dimer could be suppressed. Dropwise addition of a solution of **20** in acetonitrile over 2 h led to an increase in yield of **16a** by *ca.* 30%.[79] Following the photochemical synthesis of **16a**, the succinimide was protected with benzyl bromide in good yield to give **16b**.

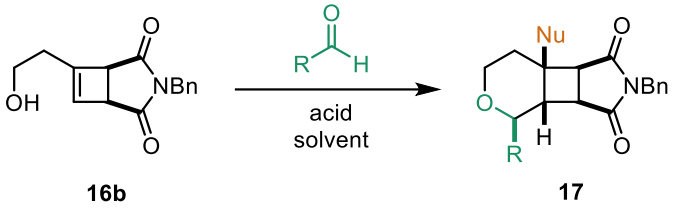


Scheme 21 – Photochemical synthesis of **16a** and undesired dimer **21**. (a) – BnBr, K_2CO_3, TBAI, acetone, Δ

2.3.2. Reagent Screening

As a starting point for this investigation several conditions that have been previously reported for Prins cyclisations were attempted.[48] Both Lewis and Brønsted acids were screened for the Prins reaction of **16b** with either benzaldehyde or hydrocinnamaldehyde and various nucleophile and solvent combinations (Table 2). It was clear that for the cyclisation of **16b** to take place, a strong protic acid was needed, as only trifluoromethanesulfonic acid or tetrafluoroboric acid gave any reaction. In acetonitrile, the Prins–Ritter product was observed, with acetonitrile acting as the nucleophile before hydrolysis on workup to give the amide product in good yield. Using tetrafluoroboric acid (HBF_4), the fluorinated product was isolated in 36% yield.

Table 2 – Acid screening for the Prins cyclisation of **16b** to give products with the general structure **17**



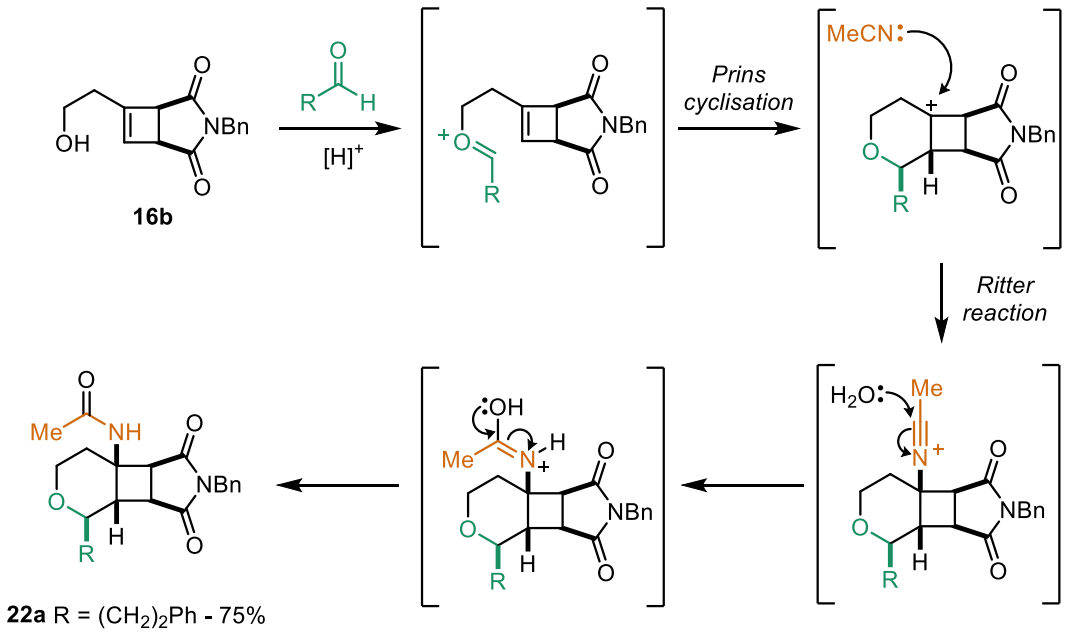
16b **17**

entry	acid	nucleophile	R	solvent	temp / °C	yield (%)
1	TFA	TFA	$(CH_2)_2Ph$	CH_2Cl_2	-40	0
2	$BF_3.Et_2O$	n/a	$(CH_2)_2Ph$	CH_2Cl_2	rt	0
3	BF_3, AcOH, TMSOAc	AcOH	$(CH_2)_2Ph$	CH_2Cl_2	rt	0
4	TfOH	MeCN	$(CH_2)_2Ph$	MeCN	rt	75
5	TfOH	AcOH	Ph	AcOH	rt	0[a]
6	HCl	Cl^-	Ph	CH_2Cl_2	rt	0
7	amberlyst-15	n/a	Ph	-	80	0
8	HBF_4	F^-	Ph	CH_2Cl_2	rt	36

In all cases, 1 equivalent of aldehyde and 1.2 equivalents of acid were used. [a]Major product isolated was the acetylated starting material **16b**. All other reactions gave only recovered starting material.

The Ritter reaction proceeds by the nucleophilic addition of a nitrile to a suitable electrophile such as a carbocation (Scheme 22). The resulting nitrilium ion is then hydrolysed by water to give the desired amide. Prins-Ritter reactions to form 4-amidotetrahydropyrans were first reported by Willis *et al.*[80] and in recent years methods have been developed for the synthesis of 4-amidopiperidine derivatives and 2,6-disubstituted tetrahydropyrans using a Sakurai-Prins-Ritter variation.[81–87]

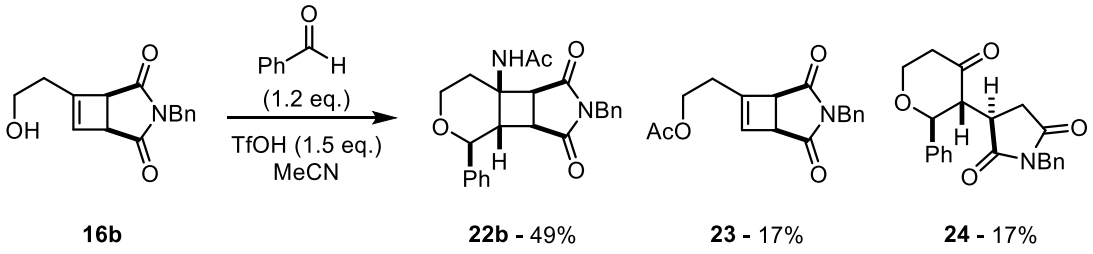
In the most successful example from the screen of Prins reaction conditions (Table 2, Entry 4) the Prins-Ritter reaction gave amide **22a** in 75% yield and as a single diastereomer (Scheme 22). The stereochemistry of the resulting products is discussed in Section 2.3.6.



Scheme 22 – Mechanism of the Prins-Ritter reaction of **16b** to give amide product **22a**

2.3.3. Mechanisms of Side-Product Formation

With successful conditions for the formation of **22a** in hand, expansion of the scope of the reaction was desired. Despite the excellent yield obtained with the initial reaction conditions and hydrocinnamaldehyde to give **22a**, other aldehydes, such as benzaldehyde, gave only moderate yields (33%) with the same conditions. Reaction conditions were briefly optimised using a one-variable-at-a-time (OVAT) approach. In doing so, the yield for reaction of **22b** with benzaldehyde was increased from 33% to 49% by increasing the equivalents of the aldehyde and acid to 1.2 and 1.5 equivalents respectively. However, due to the persisting variation in yield for different aldehydes, the reaction was scaled up to aid isolation of other products being formed. Along with the desired product **22b**, two major side-products **23** and **24** were isolated from the reaction of **16b** with benzaldehyde (Scheme 23) as a 1:1 mixture (34% combined yield). Further investigations were carried out to determine the origin of the side products with the aim of using this information to improve the yield of desired product **22b**.

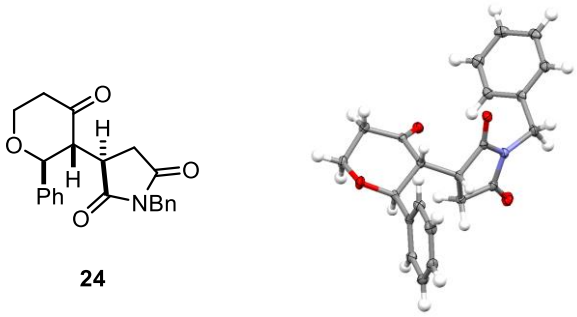


Scheme 23 – Scale up of Prins–Ritter reaction and isolation of side-products **23** and **24**

Due to the two side products being inseparable by column chromatography and present in a 1:1 mixture, it was not immediately obvious that two distinct side products were present and ADEQUATE NMR was used to elucidate their structures (Figure 5). 1,1-ADEQUATE

(Adequate DoublE QUAntum Transfer Experiment) NMR is a powerful technique for structural elucidation and provides correlations through successive $^{1}J_{CH}$ and $^{1}J_{CC}$ couplings.[88–90] ADEQUATE NMR is a proton-detected version of INADEQUATE NMR, both of which rely on the use of ^{13}C-^{13}C couplings requiring two adjacent ^{13}C nuclei, making these methods insensitive.[91,92] The proton detection of ADEQUATE NMR allows an increase in sensitivity relative to INADEQUATE NMR and also has an advantage over HMBC NMR by only showing correlations for protons and carbons exactly two bonds apart. These techniques are especially effective for molecules containing several contiguous quaternary centres and have been used in the structure elucidation of many natural products.[93]

Data obtained by ADEQUATE NMR allowed determination that the mixture consisted of two distinct structures, **23** and **24**. This was further confirmed when it was found that **24** could be isolated from the mixture by recrystallisation, allowing ^{1}H-NMR data to be obtained for each side product (Figure 6). X-ray crystallography was then used to corroborate the structure of **24** along with its relative stereochemistry (Figure 4).



24

Figure 4 – X-ray crystal structure of **24**

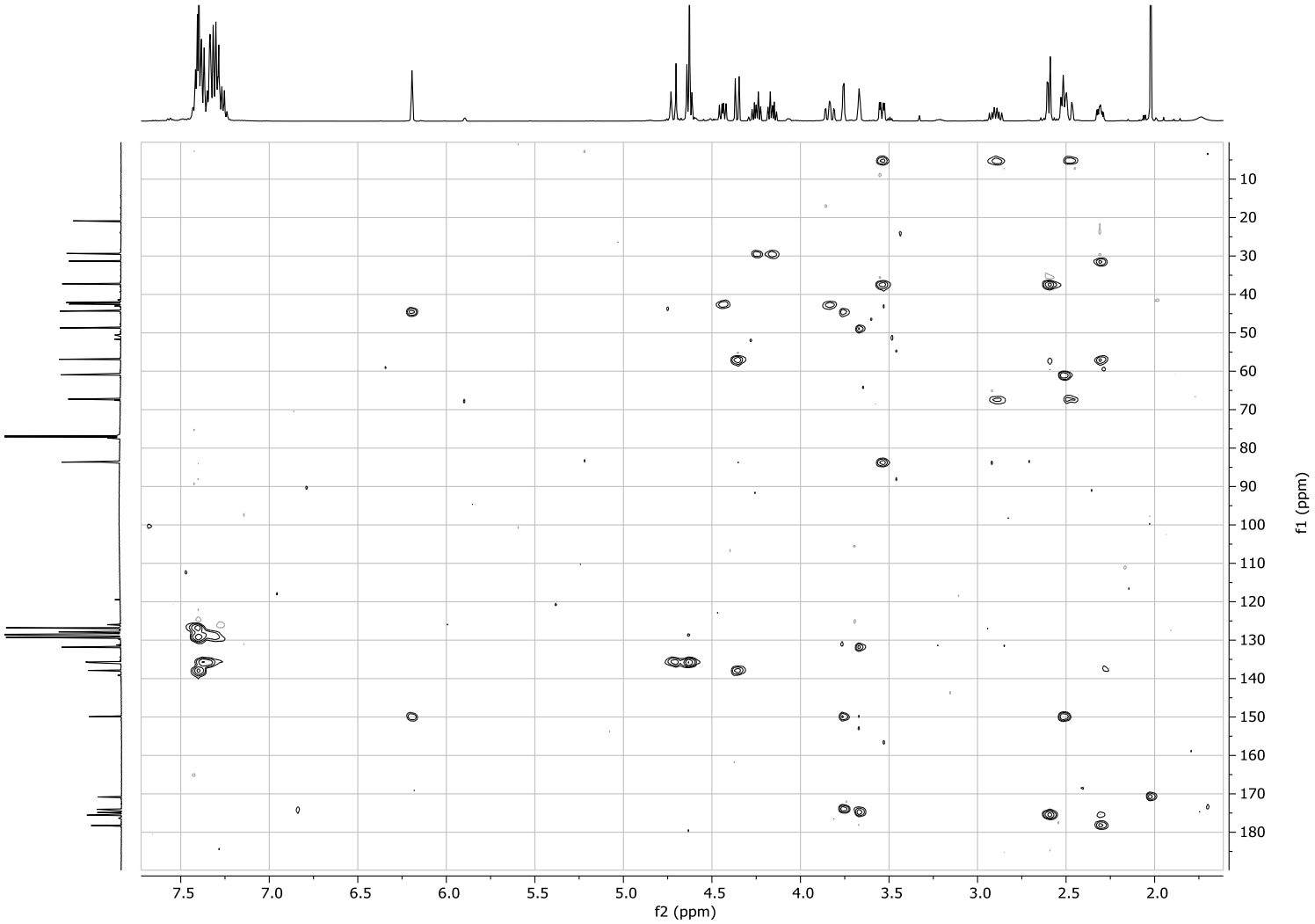


Figure 5 – ADEQUATE-NMR spectra of the 1:1 mixture of **23** and **24**

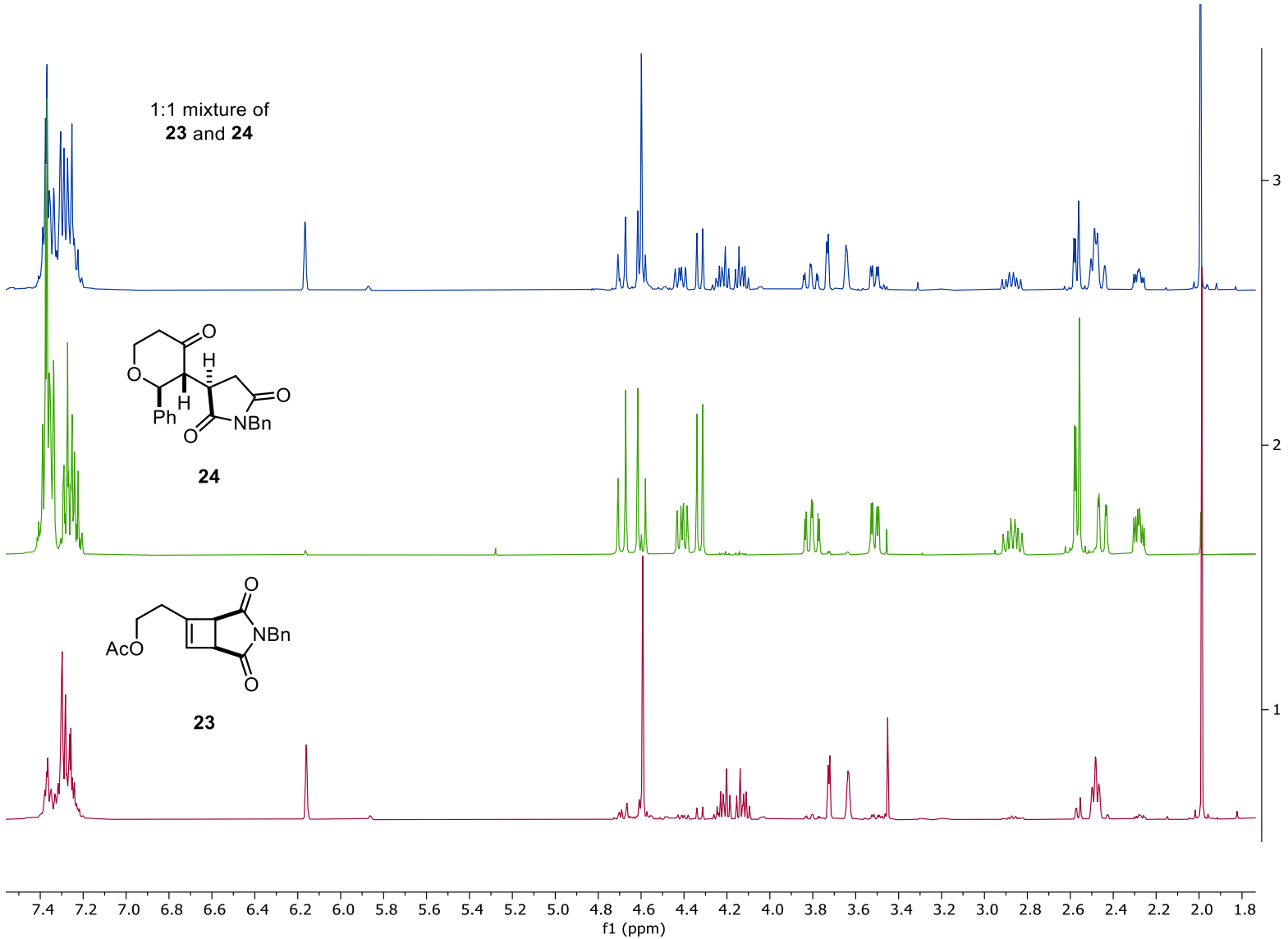
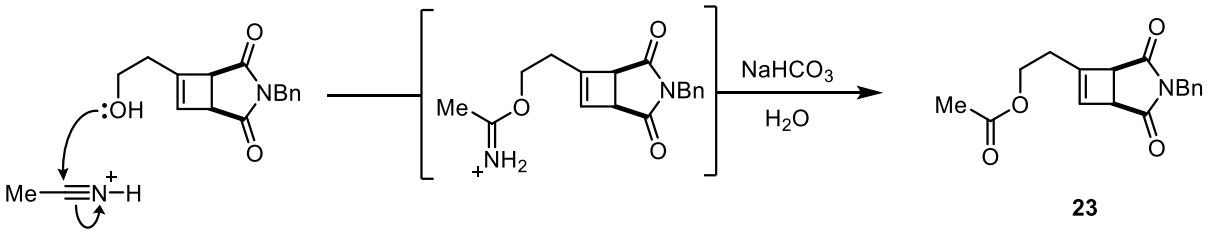


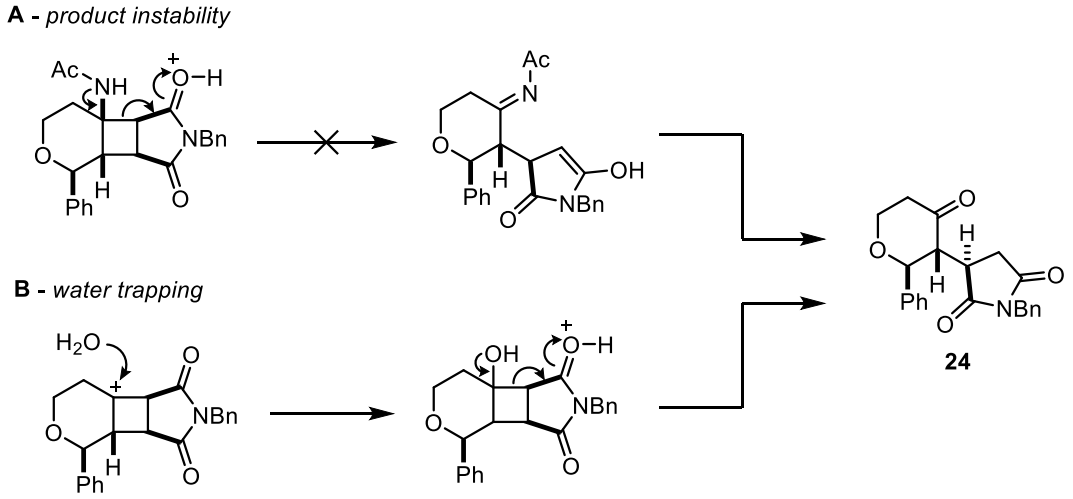
Figure 6 – ^{1}H-NMR spectra of the 1:1 mixture of **23** and **24** (top), **24** (middle) and **23** (bottom)

Acetate **23** was proposed to arise from nucleophilic attack of the starting alcohol onto the protonated acetonitrile generated in the strongly acidic reaction conditions, Scheme 24.



Scheme 24 – Proposed mechanism for the formation of acetate **23**

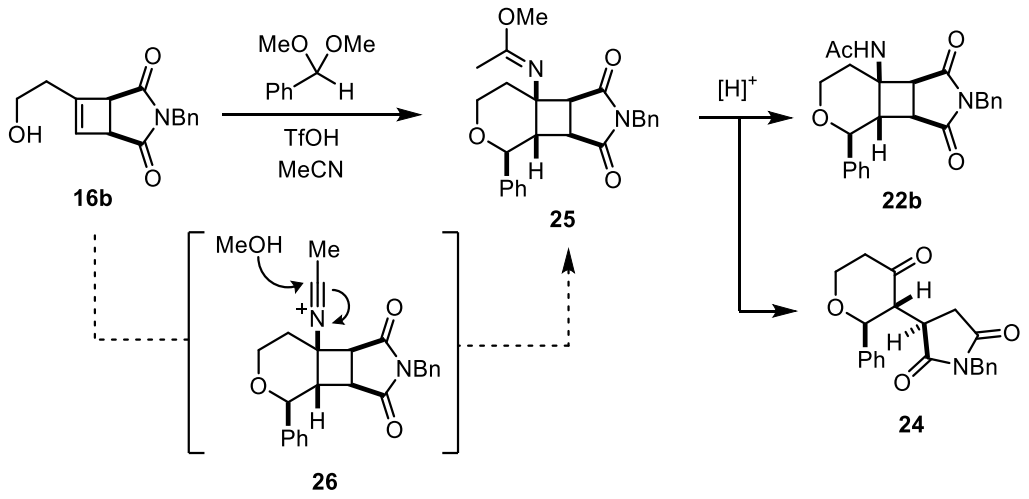
Formation of **24** proceeds through fragmentation of the central cyclobutane ring, and several possible mechanisms for the fragmentation were proposed. One possibility (**A** - Scheme 25) was that the Prins–Ritter product **22b** is unstable to the reaction conditions, and the ketone **24** forms because of fragmentation of the product. Resubjecting **22b** to the reaction conditions showed no conversion to **24**, therefore confirming the stability of **22b** in the presence of triflic acid.



Scheme 25 – Possible mechanisms for the formation of **24**

The second proposed mechanism for the formation of **24**, (**B** - Scheme 25), involves addition of water to the intermediate carbocation followed by ring fragmentation of the resulting alcohol. This hypothesis was tested by repeating the reaction using rigorously anhydrous conditions, and addition of 4Å molecular sieves. However even under these conditions a small amount of **24** was still isolated. During the condensation between the alcohol and aldehyde, an equivalent of water is liberated which could be responsible for formation of side product **24**. The reaction was therefore repeated with the dimethyl acetal, which upon condensation, would produce an equivalent methanol rather than water. With these conditions, a single new product was observed by ^{1}H NMR spectroscopy and identified as the acetimidate **25** (Scheme 26). It is proposed that **25** is formed through a Pinner reaction[94–96] of methanol with the intermediate

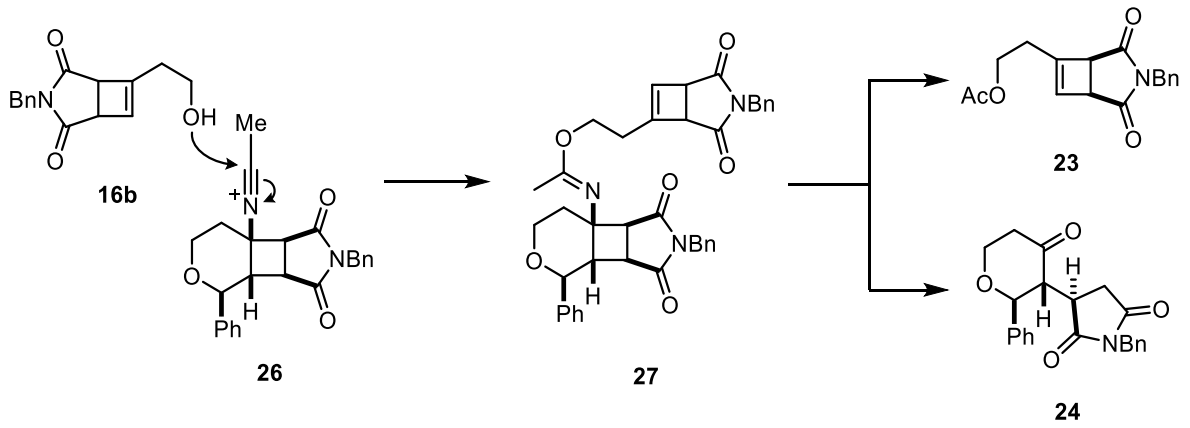
nitrilium ion **26**. When exposed to silica gel for purification by column chromatography, **25** degraded to give both the desired product **22b**, and the ketone side product **24**. This degradation also occurred when **25** was left in $CDCl_3$ for 3 days, indicating that the fragmentation of **25** to **24** requires only mildly acidic conditions.



Scheme 26 – Isolation of acetimidate **25** and potential mechanism for formation of **24**

Formation of the **24** through degradation of the acetimidate **25** was feasible for Prins reactions using acetals, however this did not provide an explanation for its formation in the absence of methanol. If water is instead formed from the condensation, nucleophilic addition of water to the nitrilium ion simply results in formation of the product, which has been proven stable to the reaction conditions.

During work undertaken at AstraZeneca (PT&D, Macclesfield) the mechanism of the formation of **24** was further investigated and the reaction conditions optimised. Initially reaction profiling was carried out using UHPLC, with standards of **22b**, **23** and **24** used and samples taken at 1, 2, 5, 10 and 20 minutes. The results indicated that the reaction was fast, with no starting material observed after one minute and subsequent samples showing no change in the ratio of products. Despite being observed when conducting the reaction previously, comparison of the crude reaction material to known standards of **23** and **24** confirmed that they were not present in the reaction mixture, however a new peak (m/z 644) was observed. ^{1}H-NMR data of the crude reaction mixture showed presence of the desired product **22b**, as well as signals for an unidentified product, very similar, but not identical, to the starting material **16b** and product **22b**. Comparing this spectrum with previous data from similar crude reactions, the unidentified product had also been formed previously, however not in any appreciable amount and had never been isolated. The new product (m/z 644) was identified as acetimidate **27** which was present as a 1:1 mixture of diastereomers due to the racemic nature of alcohol **16b**.



Scheme 27 – Formation of dimeric by-product **27** and its hydrolysis to give **23** and **24**

Upon re-evaluation and comparison of the ^{1}H-NMR of the crude material from previously performed reactions, small amounts of **27** had been formed as a by-product, however had never been isolated. In this case, **27** was then purified using alternative methods[i] allowing its structure to be confirmed by 2D-NMR and HRMS.

Formation of **27** in the reaction mixture results from attack of the nitrilium ion by another molecule of the cyclobutene alcohol **16b** in a Pinner reaction to form the carboximidate **27** (Scheme 27).[97] This result is analogous to a previous reaction carried out with benzaldehyde dimethyl acetal, in which a carboximidate **25** was formed by a similar mechanism when methanol was present in the reaction mixture. This demonstrates that although an alcohol was not being formed in the reaction, as an alcohol, the starting material can act in a similar fashion to form **27**.

Dimer **27** was stirred with silica gel resulting in recovery of **27** (60%) and isolation of a 1:1 mixture of **23** and **24** (30%). This interesting outcome indicates that dimer **27** is a precursor to side-products **23** and **24**. The instability of **27** to certain column chromatography conditions explains why it was never previously isolated, and only observed as its degradation products **23** and **24**. The dimer **27** was also found to be unstable to more forcing hydrolysis conditions (e.g. aq. HCl).

With this information in hand, a method to prevent formation of **27** and therefore **23** and **24** was desired. This was achieved by changing the order of addition of reagents. Previously alcohol **16b** was dissolved in solvent and the aldehyde and acid then added. By adding a solution of **16b** dropwise to a solution of the aldehyde and acid, the local concentration of **16b**

[i]Automated column chromatography (CombiFlash) on silica using *tert*-butylmethylether (TBME) and *iso*hexanes as solvent was used. The change in solvent from what had been used previously was due to the UV absorbance of ethyl acetate (cut-off 210 nm) which would interfere with UV detection of products of this reaction which absorb most strongly at 220 nm. TBME is similar in polarity to ethyl acetate so it was therefore assumed that this would not have a great impact on separation.

in the reaction mixture was minimised and this resulted in complete inhibition of formation of **27**. However, the yield of **22b** did not substantially increase, and further work to optimise the reaction conditions was therefore necessary.

2.3.4. Design of Experiments Optimisation

Design of Experiments (DoE) is a systematic approach to data collection that allows generation of valid statistical conclusions when considering trends in data sets. Traditionally, reaction optimisation is carried out through a one-variable-at-a-time (OVAT) approach in which variables are individually varied whilst all others are kept constant (Figure 7). This method has several pitfalls; it can often result in missing the 'true optimum' by limiting coverage of the design space, it is experimentally inefficient, and does not consider interactions between factors. DoE allows for a more thorough investigation into a wider range of results and therefore often gives more detailed insight into the reaction.

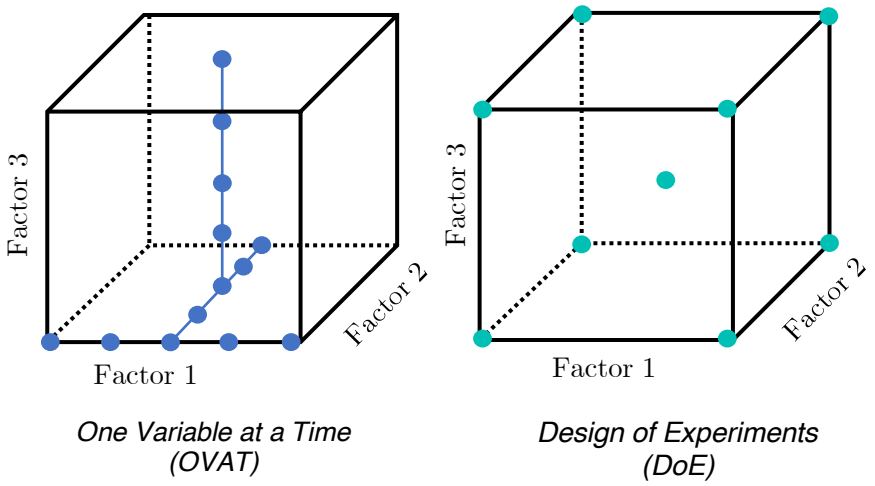


Figure 7 – Representation of the difference between OVAT and DoE optimisation

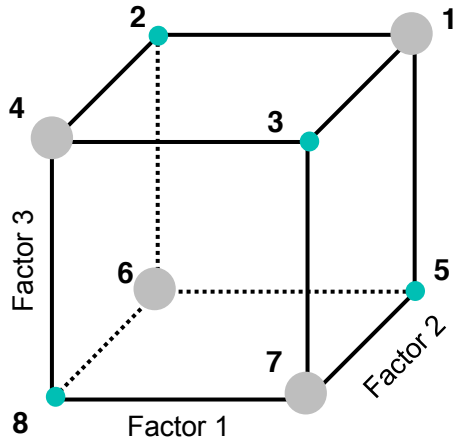
In DoE, combinations of the extreme value of each factor are investigated (represented by corners of a cube) as well as at the centre point for all factors (Figure 7). Factors are chosen based on prior knowledge of the reaction and appropriate high (H) and low (L) levels set. Responses are also chosen (usually percentage yield or selectivity) and methods for the consistent collection of data outlined. It is important that experiments are carried out in as consistent manner as possible to minimise experimental error, however experiment replicates (usually at the centre point) allow some experimental error to be accounted for by the model. Nuisance factors such as temperature, time, batch of materials, etc. must be closely controlled, and this is often aided by randomising the order in which experiments are carried out.

One major advantage of DoE is the small number of experiments required to achieve a significant model of the reaction. The number of experiments varies depends on the number of factors and the type of design used. Full-factorial designs involve all combinations of factors at

all levels, whereas fractional designs cover only a specific subset of the total possible number of runs whilst retaining the maximum amount of information. Table 3 shows how a full-factorial design for three factors at two levels can be carried out in eight experiments. Carrying out a fractional-factorial design with the same factors and levels would take only four experiments (shaded in grey). Fractional-factorial designs can have the advantage of being experimentally cheaper, however they do introduce confounding into the design which can sometimes make it difficult to assign a response to an individual factor.

Table 3 – Full-factorial experimental design for 3 factors at two levels (+/-) (fractional-factorial shaded in grey).

exp no.	factor 1	factor 2	factor 3
1	+	+	+
2	-	+	+
3	+	-	+
4	-	-	+
5	+	+	-
6	-	+	-
7	+	-	-
8	-	-	-



Optimisation of the cyclobutene Prins reaction using DoE was carried out in an attempt to increase the yield of **22b**. Prior to this optimisation, the maximum yield achieved for the reaction (Scheme 23) was 49%. Based on prior experimental work, the factors chosen were; addition rate of alcohol **16b** (equiv./min), equivalents of benzaldehyde and excess of triflic acid (with respect to benzaldehyde). Addition rate was previously shown to be important to inhibit formation of the dimeric side product **27** and high and low values were chosen to ensure the widest experimental range possible was being investigated. Equivalents of benzaldehyde was also chosen as a factor as it was hypothesised that a large excess of the aldehyde could lower the local concentration of unreacted starting material **16b** and therefore also limit formation of the dimer. Equivalents of triflic acid were varied with respect to benzaldehyde and the high and low values shown indicate the excess of the reagent and not the absolute value.

Table 4 – Factors and levels chosen for first DoE (Full-factorial with 3 replicates at the centre point = 11 experiments)

	factor	units	high	low
A	amount of aldehyde	equivalents	5.0	1.2
B	excess of TfOH w.r.t. aldehyde	equivalents	1.0	0.1
C	addition rate of alcohol **16b**	equivalents min^{-1}	0.80	0.04

To keep reactions as consistent as possible, all experiments were carried out using the same equipment (syringe pump and Integrity10 reaction station) with temperature set to 25 °C and batches of all chemicals kept constant throughout, including a stock solution of **16b** in MeCN. Responses were recorded by analysing ^{1}H-NMR spectra of the reaction mixture with an internal standard 1,2,4,5-tetrachloro-3-nitrobenzene (TCNB). As well as the product yield, yields of previously identified by-products **23** and **24** were also recorded.

Once reactions had been carried out the data were analysed using the DoE software MODDE 12.1, allowing a model to be generated based on the experimental data. After refinement of the model by excluding any terms deemed statistically insignificant, it was clear that the only factor found to influence product yield was the equivalents of benzaldehyde. Figure 8 shows a coefficient plot for the data, which describes the effect each factor has on the response (percentage yield). A negative bar indicates that as the factor increases from low to high, this has a negative impact on the response, i.e. the yield is higher at the low value for benzaldehyde charge.

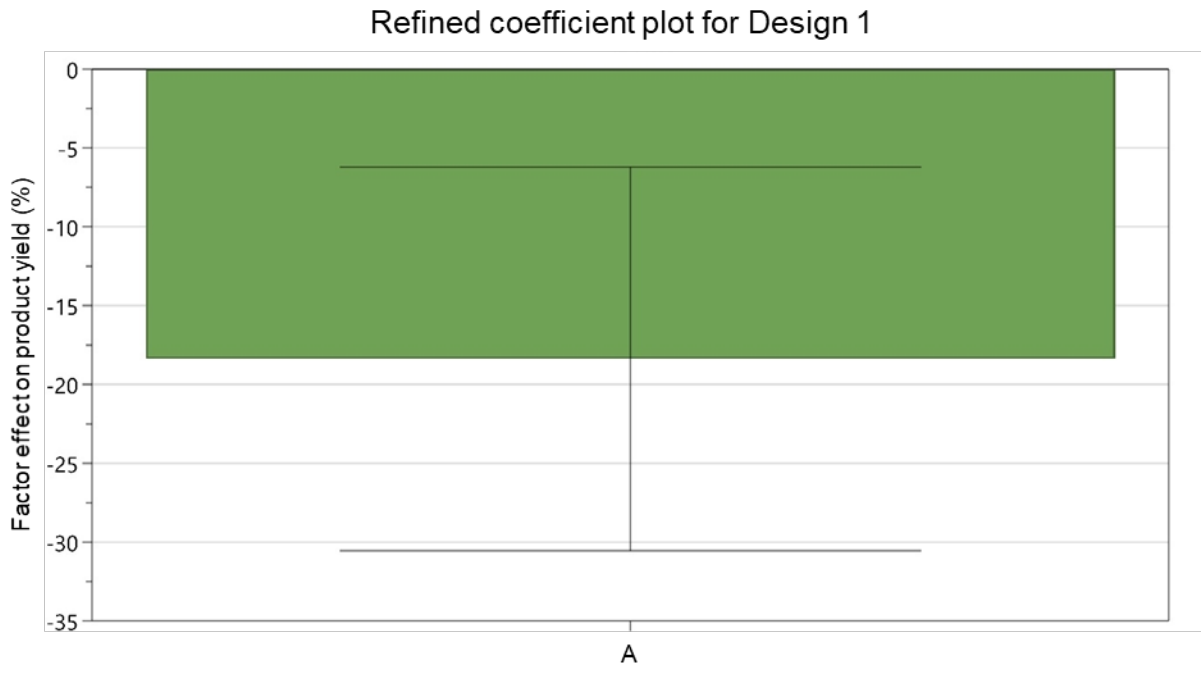
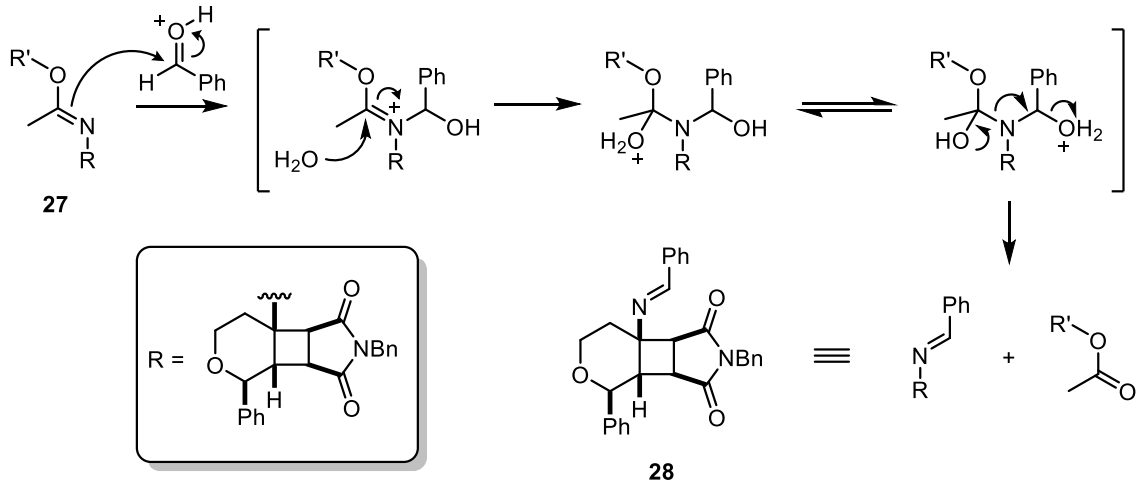


Figure 8 – Coefficients plot for Design 1 showing only benzaldehyde as a significant factor

In the experiments where benzaldehyde was at the high level, significant quantities of new imine by-product **28** were detected which could be responsible for the drop in yield. A plausible mechanism for the formation of **28** could be by reaction of the previously identified acetimidate dimer **27** with excess benzaldehyde, however this is yet to be confirmed (Scheme 28).



Scheme 28 – Proposed mechanism for the formation of imine **28**

R^2 values are used to describe the amount of variability in the results and ideally should be as close to 1 as possible. Q^2 describes the model's ability to predict results accurately and should also be close to 1 and within 0.3 of R^2. For the first DoE, $R^2 = 0.565$ and $Q^2 = 0.387$, indicating that there is some variation not accounted for by the model and that this model may not be able to satisfactorily predict results. This is also clearly shown in Figure 9 which shows how the experimental yields do not correlate with those predicted by the model.

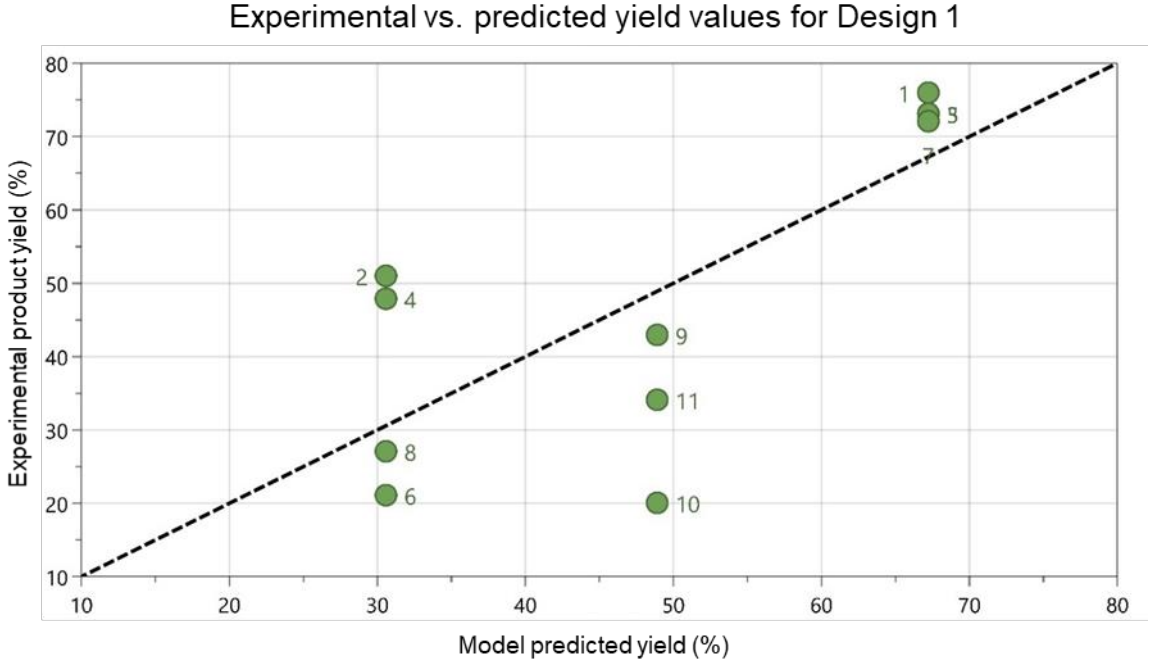


Figure 9 – Experimental vs. predicted plot for Design 1

Although the model could not be used as a predictive tool, within the experiments carried out the highest product yield obtained was 76% which was achieved at the low values of each factor (Section 4.3, Table 11– Design 1) and is a 27% improvement on the previous optimum yield. It seemed that rate of addition was not a significant factor, as the percentage yields for these experiments were comparable at low and high addition rates. For this reason, it was decided that a second design should be carried out to further lower the amount of benzaldehyde and investigate the possibility of using catalytic triflic acid.

For the second design the same factors were used, however the levels altered based on the results of the first design. Addition rate was not found to be significant at the levels chosen previously, so the design was initially fixed at the high level (i.e. 2-factor full-factorial design). It was later decided to complement this design by running the same experiments at the low level for addition rate and the data from both combined to give a 3-factor full-factorial set of results. Equivalents of benzaldehyde were reduced to H: 1.20 and L: 1.02 and the excess of triflic acid was also reduced to H: 0.0 (corresponding to equal benzaldehyde and triflic acid) and L: -0.9 (indicating a 0.9 equivalent deficit), Table 5.

Table 5 - Factors and levels chosen for second DoE (Full-factorial with 3 replicates at the centre point = 11 experiments total)

	factor	units	high	low
A	amount of aldehyde	equivalents	1.20	1.02
B	excess of TfOH w.r.t. aldehyde	equivalents	0.00	-0.90
C	addition rate of alcohol **16b**	equivalents min^{-1}	0.80	0.04

Analysis of the results using MODDE gave a model for these data that included significant interaction terms, one between benzaldehyde and triflic acid charges, and another between triflic acid excess and addition rate. These significant interactions mean that the individual terms for addition rate and benzaldehyde charge cannot be eliminated from the model even though their error bars render them statistically insignificant. It is clear from Figure 10 that the factor contributing most strongly to a change in response is the triflic acid excess, showing that having this factor at the high level (0.00 equivalents excess w.r.t. aldehyde) has the average effect of increasing product yield by *ca.* 27%. This therefore indicates that the reaction is not able to proceed catalytically, and the best results are observed with stoichiometric acid.

R^2 (0.977) and Q^2 (0.912) values for this data set were excellent showing that experimental variability is well accounted for by the model and it can be used for the prediction of results. This was also indicated by the observed *vs.* predicted plot which shows close alignment between experimental results and model prediction (Figure 11). Formation of imine **28** in this design

was extremely low with all experiments giving $< 4\%$. Formation of by-products **23** and **24** was observed in some reactions; however, no model could be generated based on the data collected and again, only the product **22b** yield was analysed as a response.

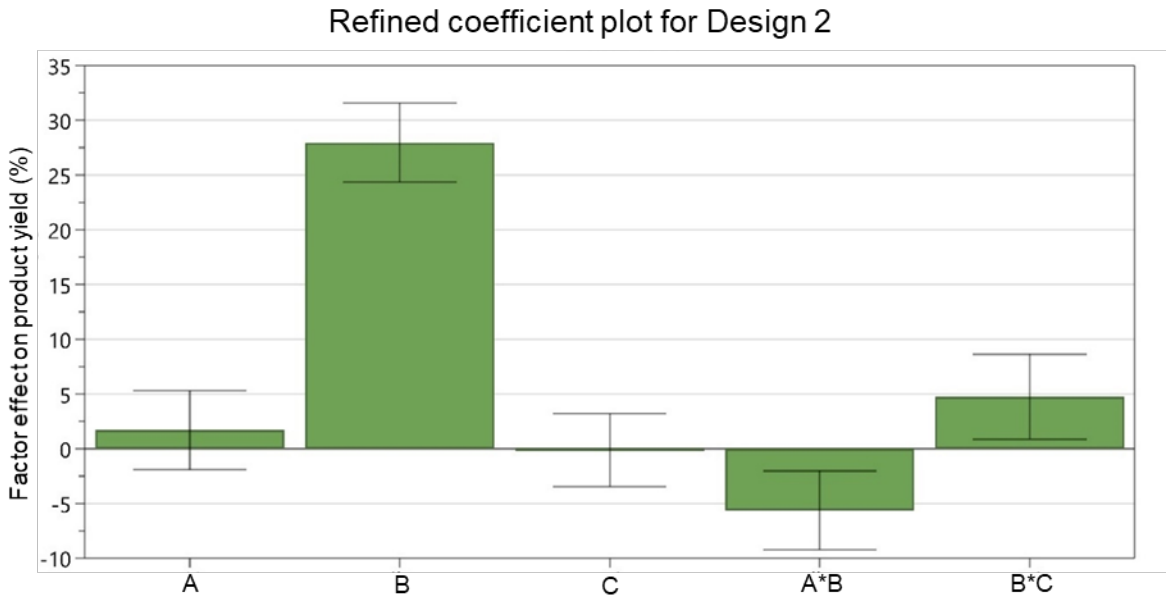


Figure 10 - Coefficients plot for the second DoE showing triflic acid excess as the most significant factor

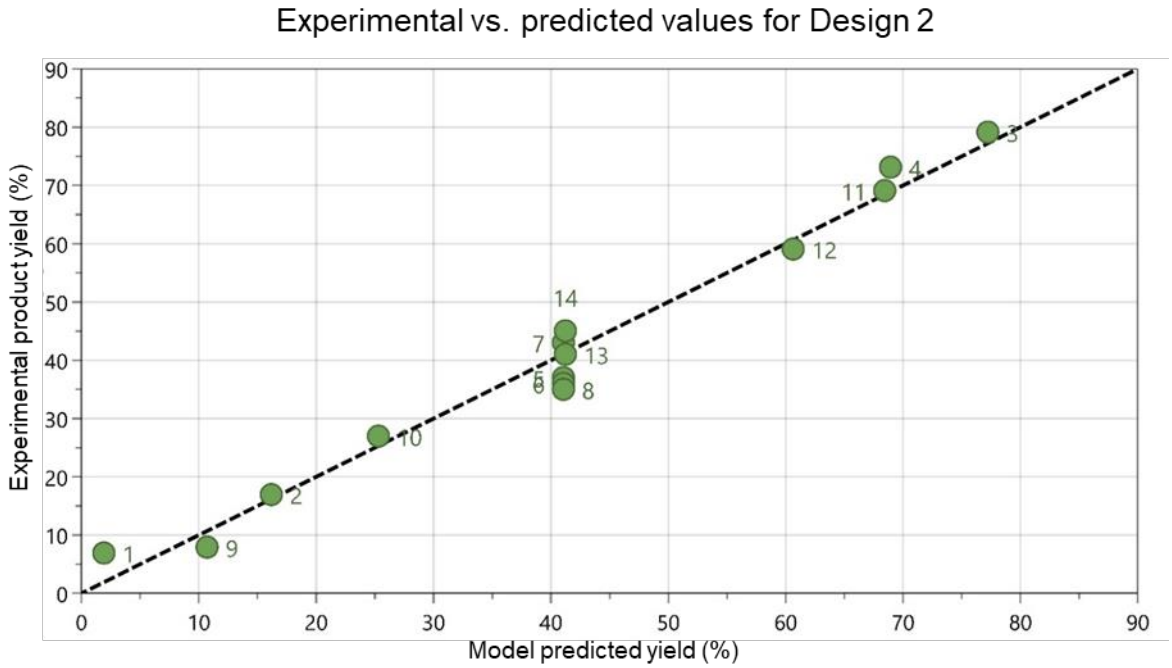


Figure 11 - Experimental vs. predicted plot for Design 2

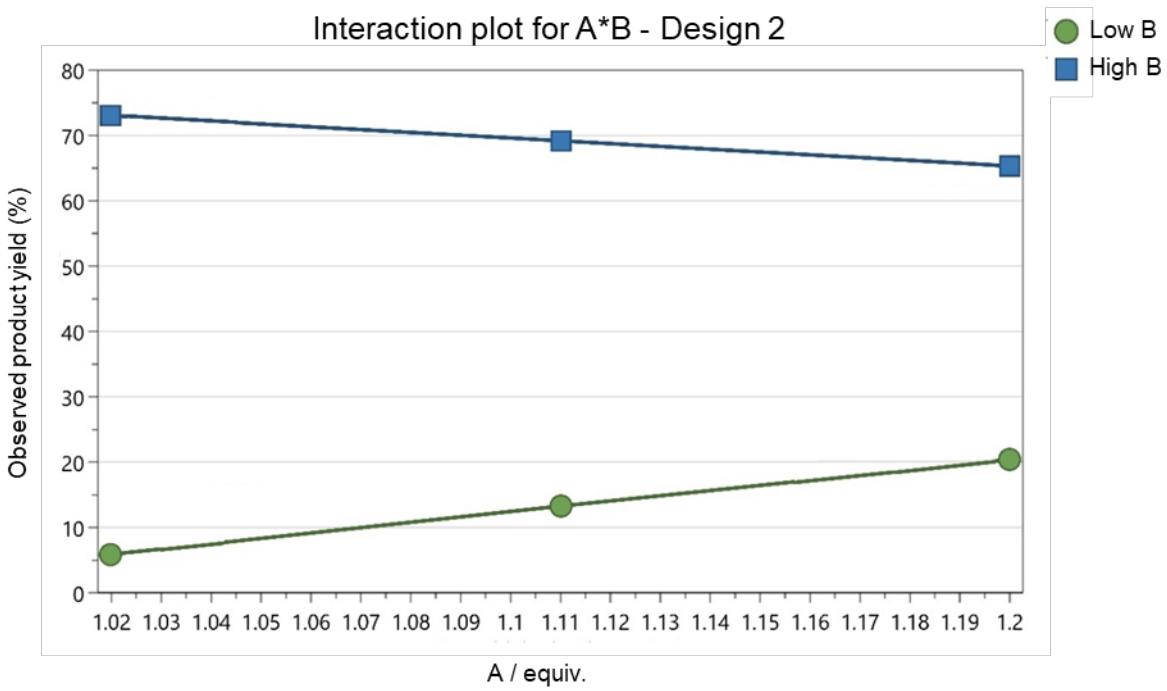


Figure 12 – Interaction plot for benzaldehyde charge and triflic acid excess (A*B)

Interaction factors were also found to be present in the model, meaning that the effect of one variable may not be the same at all levels of another variable. In this case, interaction factors were found between the benzaldehyde charge and triflic acid excess (A*B) and between triflic acid excess and addition rate (B*C).

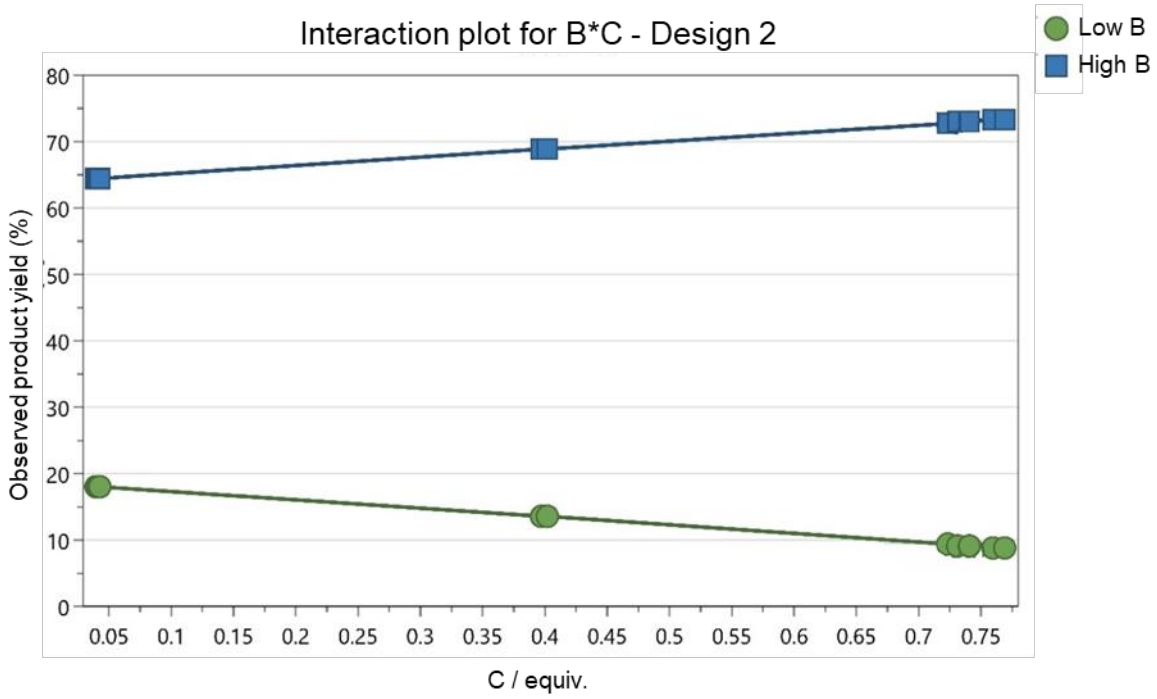


Figure 13 – Interaction plot for triflic acid excess and addition rate (B*C)

Interaction plots can be a helpful way of representing the data as shown in Figure 12 (A*B) and Figure 13 (B*C). For A*B, the general trend indicates that percentage yield is highest at

the high level of triflic acid excess, however the non-parallel lines indicate the interaction with benzaldehyde charge, i.e. triflic acid excess has a different effect at high and low levels of benzaldehyde charge. At the low level of triflic acid excess, a higher benzaldehyde charge is beneficial, however the reverse is true at the high triflic acid level. Although an interesting subtlety to this reaction, the yield is consistently higher at the high level of triflic acid and therefore any effect at the low level is insignificant with respect to yield optimisation. Similar analysis can be drawn from (B*C, Figure 13) where the triflic acid excess has a different effect on the yield at high and low levels of addition rate. Again, this is a rather subtle interaction, and the product yield is consistently higher when triflic acid is at its high level.

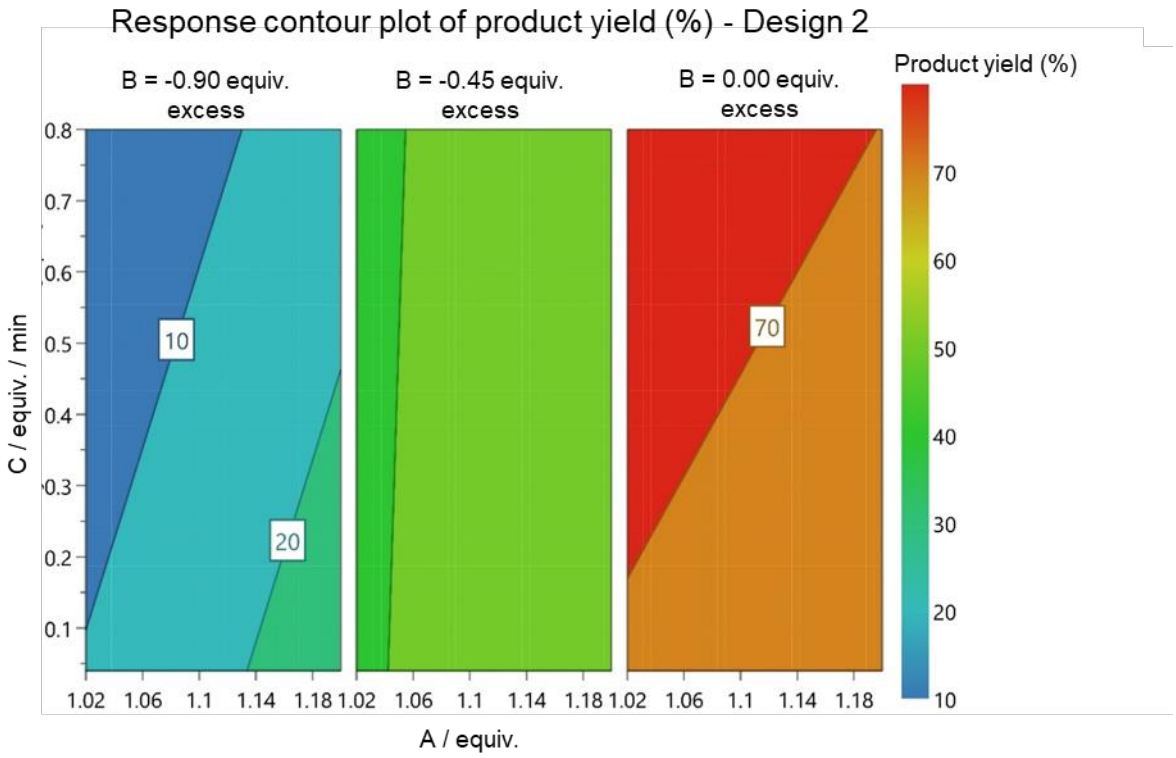


Figure 14 – Response contour plot for the three factors in the second design

Response contour plots, Figure 14, represent all interactions between factors. The far-left block shows the low yield achieved at the low level of triflic acid and shows how this changes slightly with changes in the other two factors. Similarly, the far-right block (high triflic acid level) shows the best yields with slight changes depending on levels for the other two factors.

Table 6 - Optimum conditions for OVAT and DOE optimisation

	A - benzaldehyde / equiv.	B - triflic acid excess / equiv.	C - addition rate of 16b / equiv. min^{-1}	yield 22b (%)
OVAT	1.20	0.30	-	49
Design 1	1.20	0.10	0.04/0.80	76/73
Design 2	1.02	0.00	0.04/0.80	69/79

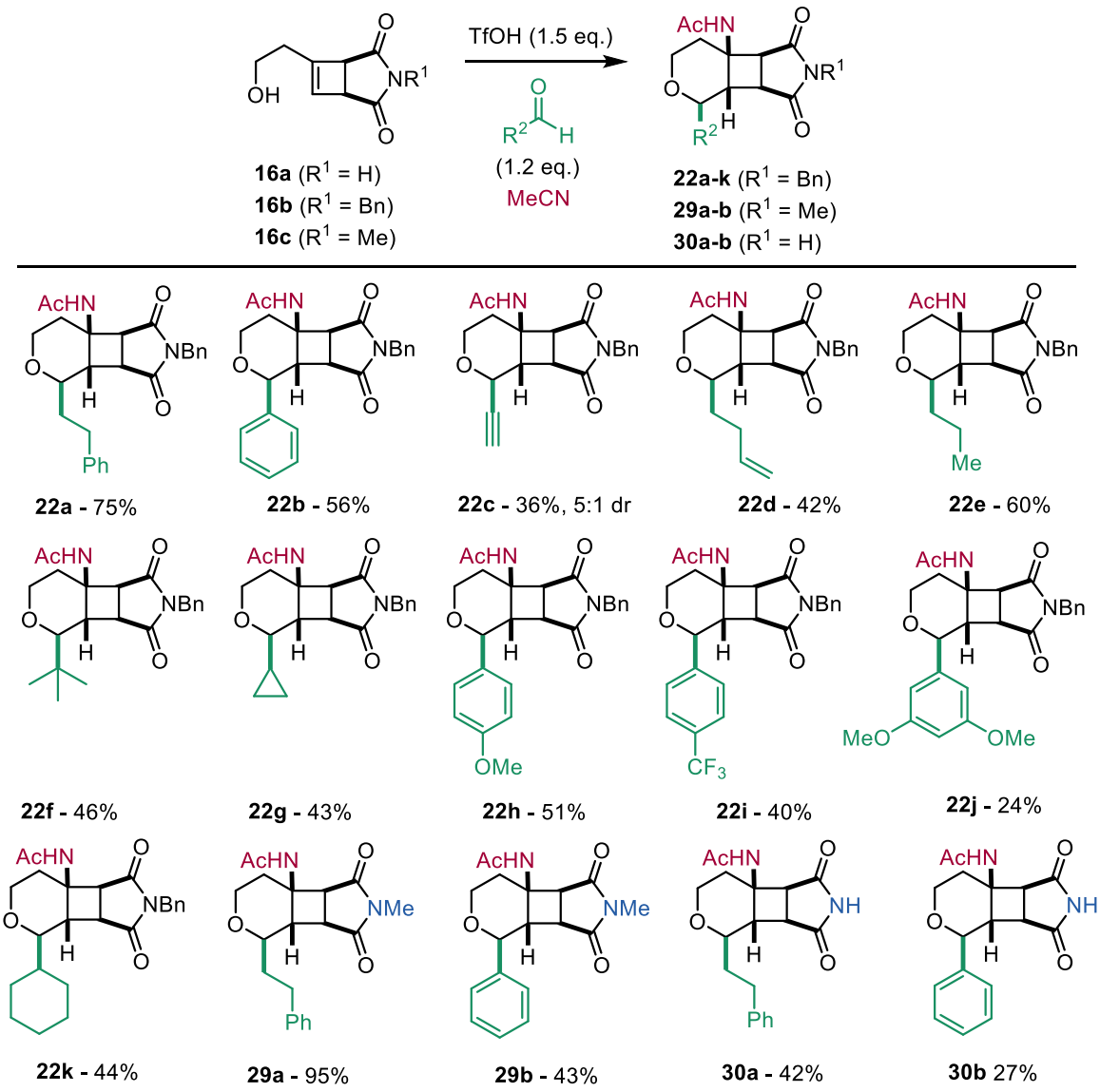
Overall, this design highlighted some interesting interaction results and fundamentally proved that stoichiometric acid is necessary for achieving optimum yields. Despite Design of Experiments often allowing prediction of optimum results based on experimental data, in this case the best results found were close to the feasible limits of the reaction – predictions of sub-stoichiometric benzaldehyde giving higher yields lacks chemical sense. Therefore, extrapolation of these results would not give any meaningful improvement in yield. Optimum yields from this set of data gave similar conditions to the previous design, with the best result achieving a modest improvement to 79% overall yield and these conditions were therefore taken as the overall optimised conditions for this reaction, representing a 30% increase in yield vs. OVAT optimisation (Table 6).

2.3.5. Reaction Scope

The scope of this Prins–Ritter reaction was investigated by performing the reaction with a range of aldehydes giving the tricyclic products **22a-k** with excellent diastereoselectivity (Scheme 29).

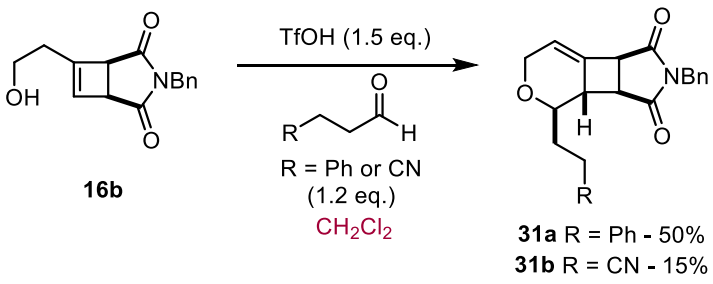
Generally good yields (24-95%) were achieved, with longer aliphatic chain aldehydes giving slightly higher yields. As well as the *N*-benzyl protected starting material, the reaction was carried out with both the *N*-methyl and the unprotected maleimides, **16c** and **16a** respectively. Whereas the reaction of **16c** with hydrocinnamnaldehyde gave **29a** in 95% yield, the analogous reaction with benzaldehyde gave **29b** in a moderate yield of 43%. The reaction was also successful with an unprotected maleimide, however the yields for both products **30a** and **30b** were significantly lower. No Prins products were isolated using ketones such as acetone and cyclohexanone.

By replacing the nucleophilic solvent acetonitrile with dichloromethane, the major product was alkene **31a**, formed by elimination of the β-hydrogen (Scheme 30). This type of elimination is known, but rarely seen in Prins cyclisations due to the slow nature of the elimination step.[98] In this case, the cyclobutane could promote the elimination by destabilising the carbocation as it cannot achieve the optimal bond angles for an sp^2 carbocation.



Scheme 29 – Scope of the Prins–Ritter reaction of maleimides 16a, 16b and 16c (unless specified, dr > 20:1, stereochemistry given for the major diastereomer)

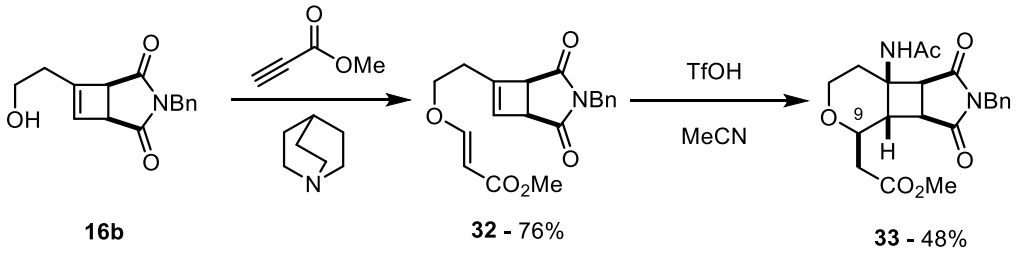
An aldehyde with a nitrile tether, 3-cyanopropanal, was also used under these conditions to determine whether an intramolecular Ritter reaction would occur (Scheme 30). However along with degradation, the elimination product **31b** was isolated in 15% yield.



Scheme 30 – Synthesis of dihydropyrans **31** in the absence of a nucleophilic solvent

The cyclobutene Prins reaction was also found to be successful using enol ether **32**; based on reactions previously used in total syntheses by Willis and coworkers.[99–101] Enol ether **32** was synthesised by reaction of **16b** with methyl propiolate under basic conditions (Scheme 24).

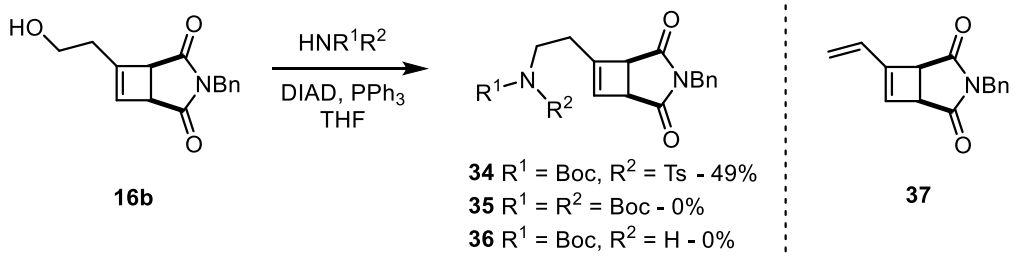
Subjecting **32** to the cyclisation conditions, gave the Prins–Ritter product **33** in 48% yield. This demonstrates the ability to introduce sidechains at the *C*-9 that have the potential for further functionalisation. Using aldehydes with more reactive side-chains directly in this Prins–Ritter reaction, such as nitriles or ketones was found to be unsuccessful.



Scheme 31 – Alternative mode of cyclisation via enol ether **32**

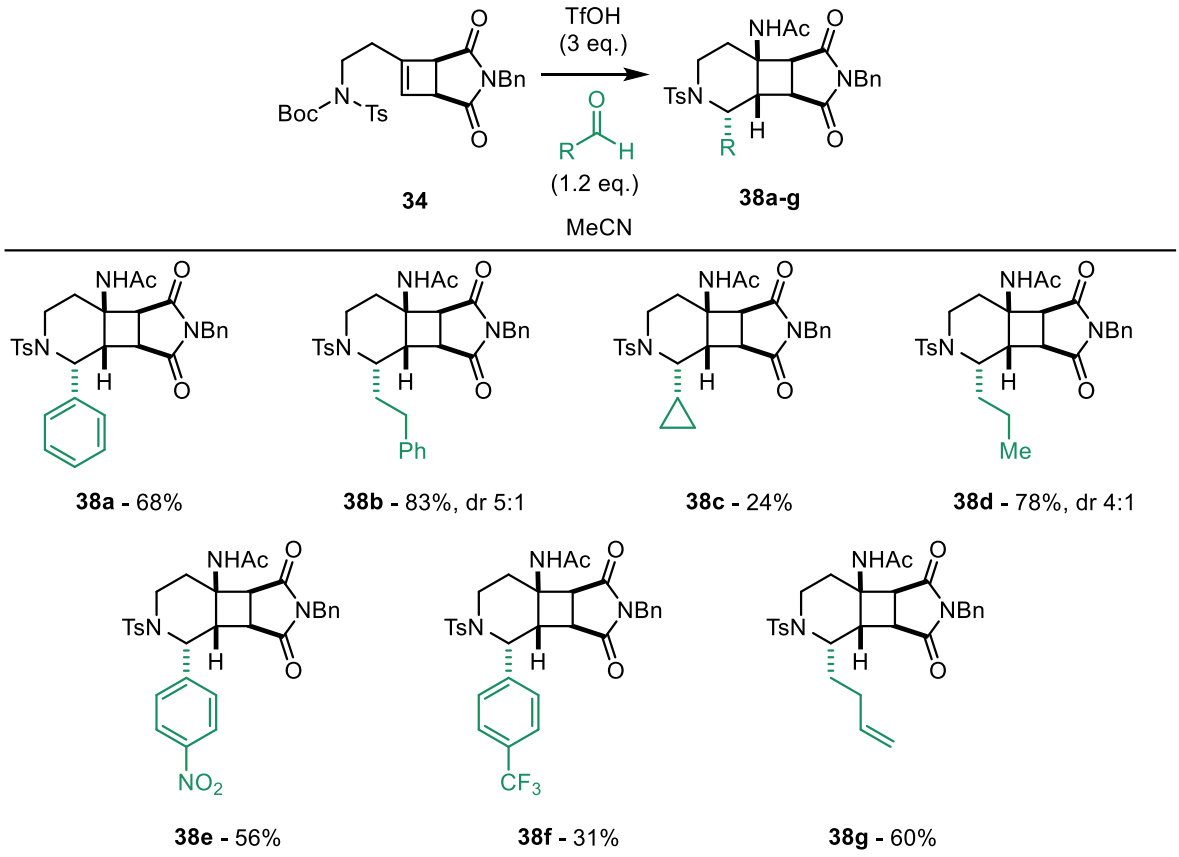
2.3.5.1. Aza-Prins Cyclisation of Cyclobutenes

As well as the Prins–Ritter reaction, the possibility of an analogous aza-Prins reaction was investigated based on previous literature success in this area.[81,87,102,103] The substrate **34** was synthesised by Mitsunobu reaction of the alcohol **16b** with a protected amine. Carbamate protecting groups were considered ideal, as it was expected that they would deprotect *in situ* under the Prins–Ritter reaction conditions. *t*-Butyl tosylcarbamate was found to be optimal for this reaction, giving the protected amine **34** in a 49% yield. Attempts to form the carbamates **35** and **36** using *t*-butyl carbamate and di-*t*-butyl carbamate respectively both gave the eliminated product **37**, Scheme 32.



Scheme 32 – Synthesis of protected amines for the aza-Prins reaction

For the aza-variation of the cyclobutene Prins–Ritter reaction, **34** was first treated with an equivalent of trific acid, allowing clean deprotection of the carbamate in just 5 minutes. This was followed by addition of hydrocinnamaldehyde and a further equivalent of triflic acid to give the aza-Prins product **38b** in an 83% yield. With this promising result in hand, the scope of the reaction was again investigated and found to be successful for several aromatic and aliphatic aldehydes **38a-g**, Scheme 33. This reaction was also found to be diastereoselective in most cases, however the major diastereomer was found to have opposite relative stereochemistry at C-9, a result which is further discussed in Section 2.3.6.



Scheme 33 – Scope of the aza-Prins–Ritter reaction of **34** to give **38a-g** (unless specified dr>20:1, stereochemistry given for the major diastereomer)

2.3.5.2. Fluoride as a Nucleophile in the Cyclobutene Prins Cyclisation

As well as the Prins–Ritter reaction with triflic acid, the reaction was also found to proceed with HBF_4, giving the fluorinated product **39a** in 36% yield (Section 2.3.2, Table 2, Entry 8). Having determined a possible mechanism for the formation of the side-products **23** and **24**, investigation into side products formed in the tetrafluoroboric acid variation of this reaction was also carried out. It was found that despite there being no potential to form an acetimidate (due to the lack of acetonitrile) **24** still formed under these conditions. This suggests that the direct reaction of water with the intermediate carbocation, **B** - Scheme 25, might be the mechanism of formation of **24** in this reaction.

The reaction of **16b** with benzaldehyde in the presence of HBF_4 was repeated, along with the analogous reaction using the dimethyl acetal of benzaldehyde, as this would prevent water forming in the condensation step, formation of **24** should also be inhibited. Figure 15 shows the ^1H NMR spectra of the crude product for the two reactions, showing clearly that use of the dimethyl acetal gives a far cleaner reaction, with no side-product **24** observed. By using the dimethyl acetal, the yield for this reaction increased from 36 to 56%.

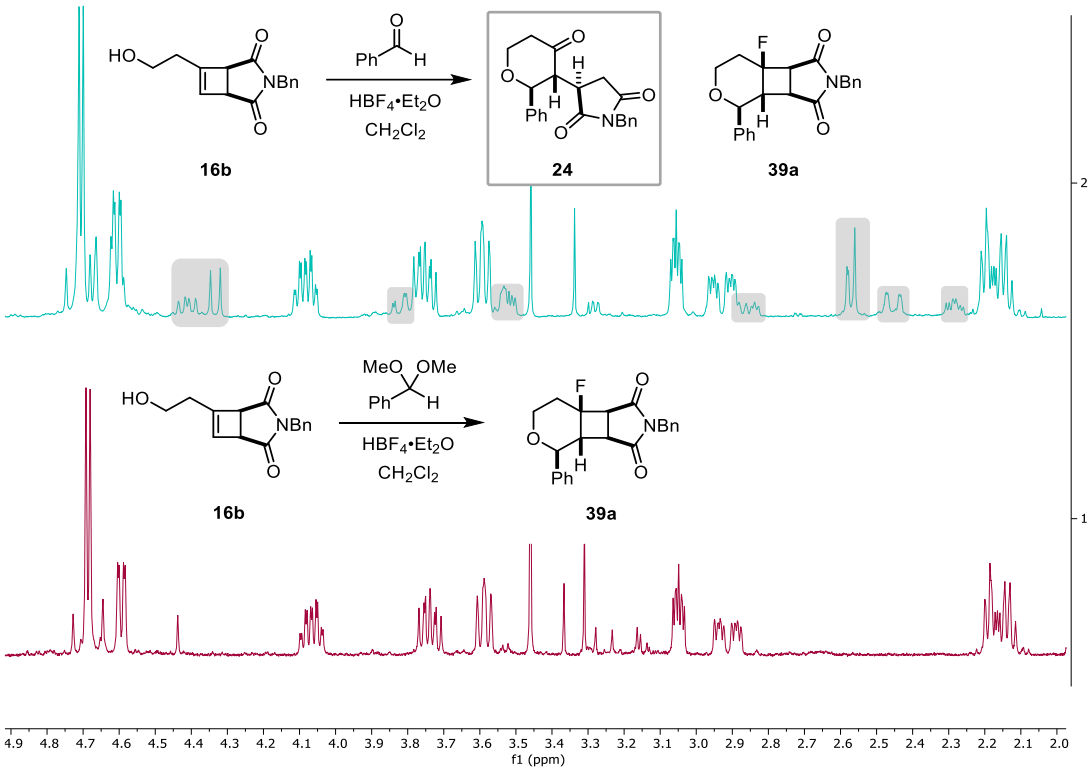
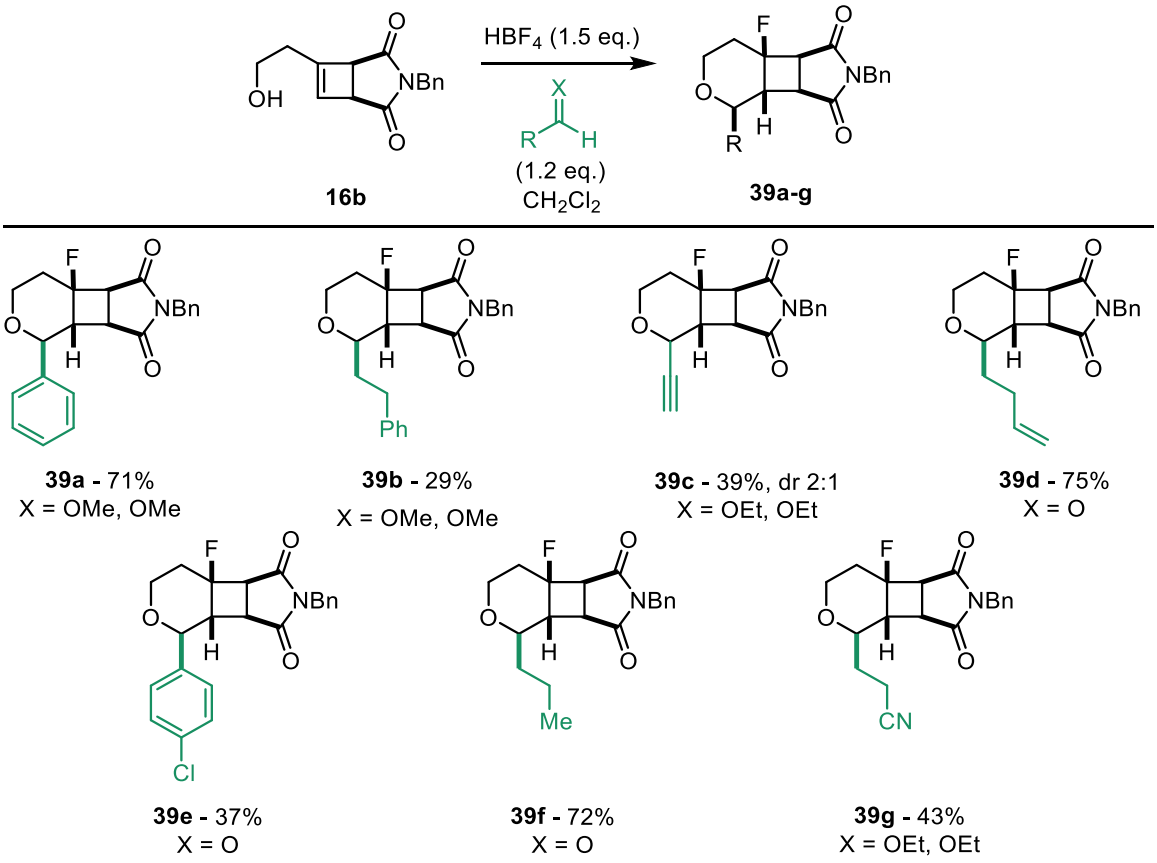


Figure 15 – ^{1}H-NMR of the reaction of **16b** with aldehyde or acetal to prevent fragmentation to **24**

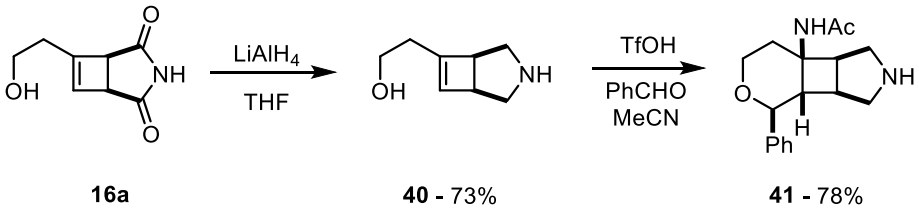
With this modification in hand, the scope of the tetrafluoroboric acid reaction was studied using dialkyl acetals, Scheme 34, giving fluoride products **39a-g**. As with the Prins-Ritter reaction, a single diastereomer was isolated in most cases.



Scheme 34 – Scope of the Prins reaction of **16b** using fluoride as a nucleophile (unless specified dr>20:1)

2.3.5.3. Prins Cyclisation of a Reduced Cyclobutene Alcohol

As an alternative method for the prevention of side product formation, the possibility of reducing the maleimide moiety was investigated. Following literature precedent[104] reduction of **16a** with $LiAlH_4$ gave pyrrolidine **40** in good yield and without the need for purification (Scheme 35).



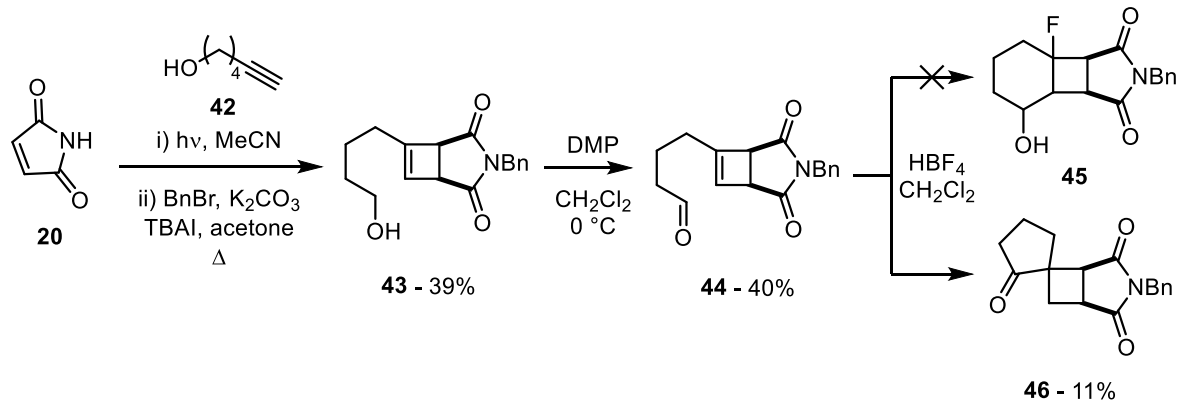
16a **40** - 73% **41** - 78%

Scheme 35 – Reduction of maleimide **16a** and application of the Prins cyclisation to the reduced substrate

Prins reaction of **40** with benzaldehyde in the presence of triflic acid gave the heterocyclic scaffold **41** in 78% yield (*cf.* 27% of **30b** formed from reaction of **16a** under analogous conditions, Scheme 29) and no significant side products detected. Reduction of the maleimide therefore offers a viable option for the optimisation of this reaction through prevention of side-product formation and reveals that it may be conducted in the presence of a secondary amine, which was unexpected given the poor yields for cyclisation with the unprotected maleimide **16a** This could allow further derivatisation of the amine.

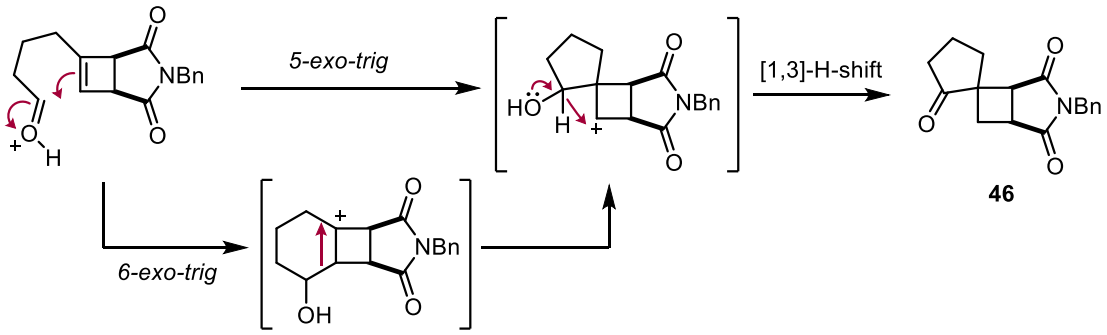
2.3.5.4. Cyclisation of Cyclobutene Aldehydes

As well as the oxo- and aza-Prins reactions previously described, it was envisaged that a carbocycle could be synthesised through reaction of the alkene with an internal aldehyde. The longer chain alkyne **42** was used for a [2+2]-photocycloaddition to give alcohol **43**. Benzyl protection followed by oxidation to the aldehyde using Dess–Martin periodinane (DMP) gave **44** (Scheme 36). It was envisaged that a *6-exo-trig* cyclisation could take place to give the Prins-type carbocation under acidic conditions, which could then be trapped by an appropriate nucleophile to give carbocycles such as **45**, analogous to the Prins products already synthesised. However, when the aldehyde **44** was treated with HBF_4, the spirocycle **46** was the major product isolated in 11% yield.



Scheme 36 – Unexpected synthesis of a cyclobutane spirocycle **46**

This reaction was further investigated by MSci candidate Matthew Holt.[79] Unfortunately, it was found that stability of the aldehyde **44** was a limiting factor in this work which prevented further optimisation of the formation of spirocycle **46**. Attempts to use Brady's reagent (2,4-dinitrophenylhydrazine) to synthesise a crystalline derivative of **46** for X-ray crystallography were also unsuccessful.



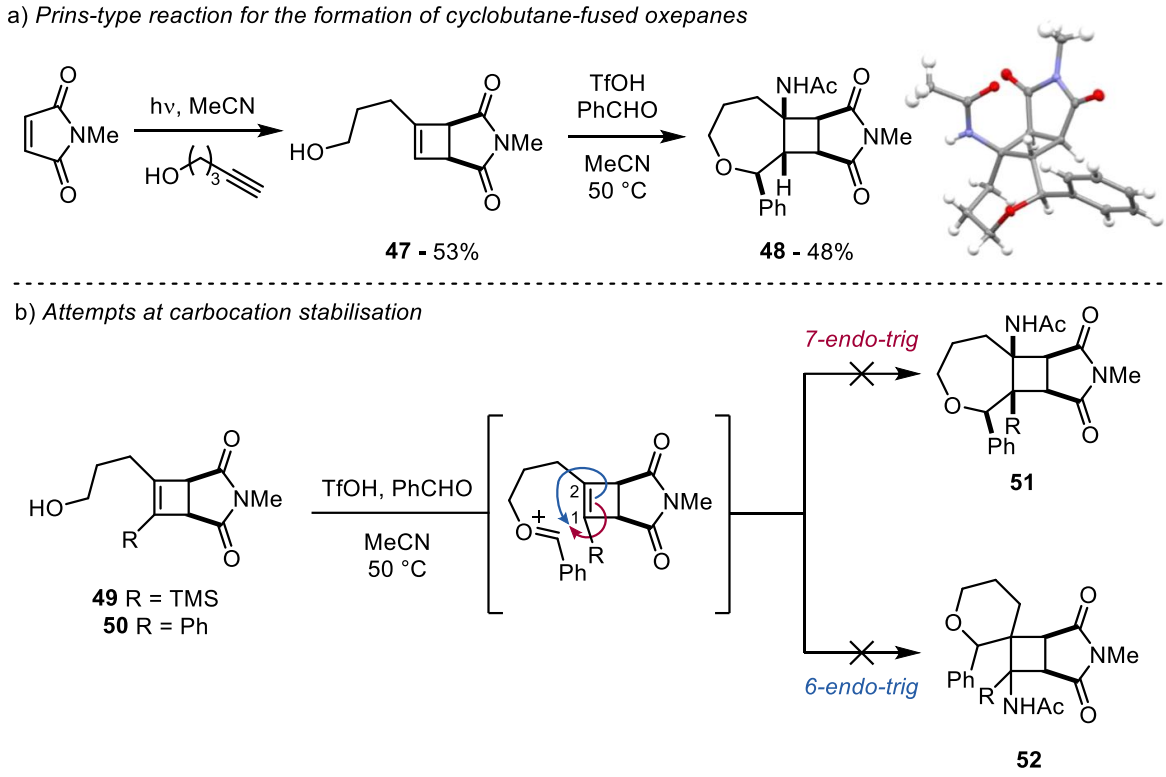
Scheme 37 – Proposed mechanism for the formation of **46**

The mechanism for the unexpected formation of **46** is currently unknown. It was reasoned that either the expected *6-exo-trig* cyclisation occurs, followed by migration or alternatively a direct *5-exo-trig* mechanism would form the same product (Scheme 37). This can then undergo a [1,3]-hydrogen shift to give **46**. Woodward-Hoffmann rules dictate that [1,3]-hydrogen shifts are disallowed under thermal conditions and therefore further evidence in the form of deuterium labelling experiments would be necessary to confirm the proposed mechanism.[105] In addition, it would be interesting to investigate the effect on chain length on the outcome of this reaction, as well as a potential acid screen for this transformation.

Insight into the reaction mechanism would provide valuable information about the potentially novel transformation happening and allow facile access to these structurally interesting compounds.

2.3.5.5. Oxepane Synthesis

Along with the formation of fused tetrahydropyrans, it was proposed that the corresponding oxepane fused cyclobutanes could be synthesised in a similar fashion. [2+2]-Photocycloaddition of maleimide with 1-hexynol gave cyclobutene **47**. Under the previously optimised reaction conditions, formation of oxepane **48** proceeded in 37% yield with 32% unreacted starting material recovered. Hence, more forcing conditions may be necessary for the reaction to proceed more successfully.



Scheme 38 – Investigations carried out by A. Phillips[106] into a) the formation of cyclobutane-fused oxepanes **48** and b) the effect of stabilising groups on this cyclisation

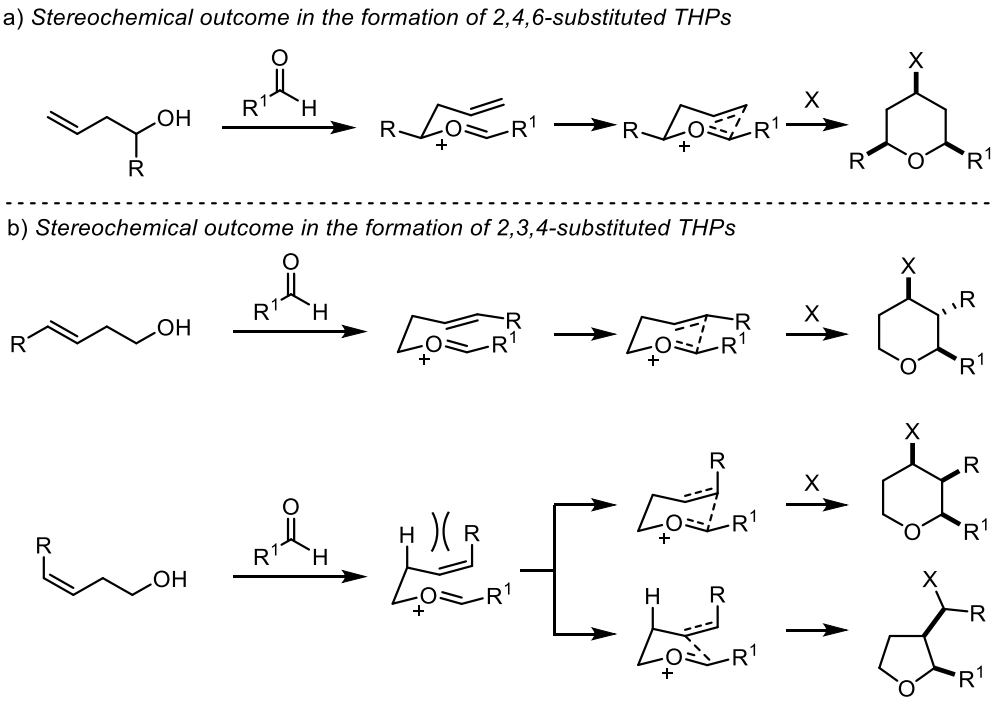
In work carried out by A. Phillips (MSci),[106] optimisation of this reaction was carried out using DoE leading to an improvement in yield of **48** from 37% to 48%. X-ray crystallography of **48** confirmed that the stereochemical outcome of the reaction was analogous to that for the tetrahydropyran work.

As an extension to this work, investigations were carried out on the effect of functional groups with the ability to stabilise or destabilise the intermediate carbocation. Cyclobutenes **49** and **50** were synthesised in a similar photochemical fashion to **47** (Scheme 38). It was hypothesised that having R = TMS (**49**) may provide a β-silicon effect and aid stabilisation of the carbocation at C-2 leading to more facile cyclisation and a faster *7-endo-trig* reaction.[107] Conversely, incorporation of a phenyl group (**50**) could theoretically provide stabilisation of a

cation at C-1 and lead instead to a *6-endo-trig* reaction. Unfortunately, cyclisation of **49** and **50** led to only formation of **48** and recovered starting material respectively.

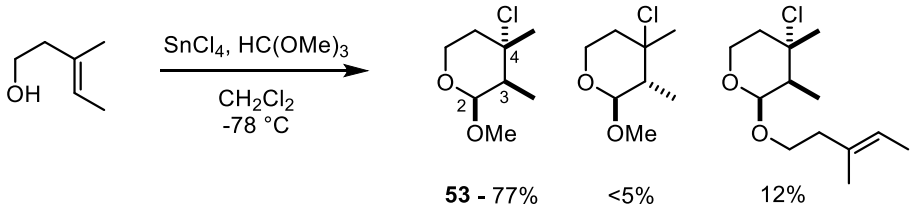
2.3.6. Diastereoselectivity

Prins reactions are known for their diastereoselectivity which arises from the nature of the chair transition state involved in the reaction mechanism. Prins cyclisations that form 2,4,6-substituted tetrahydropyrans are the most commonly reported and give the all-*cis* products due to the all-equatorial conformation in the transition state of the reaction (Scheme 39a).[108–111] Prins cyclisations forming 2,3,4-substituted THPs from primary alcohols are less common and require internal alkene starting materials.[112]



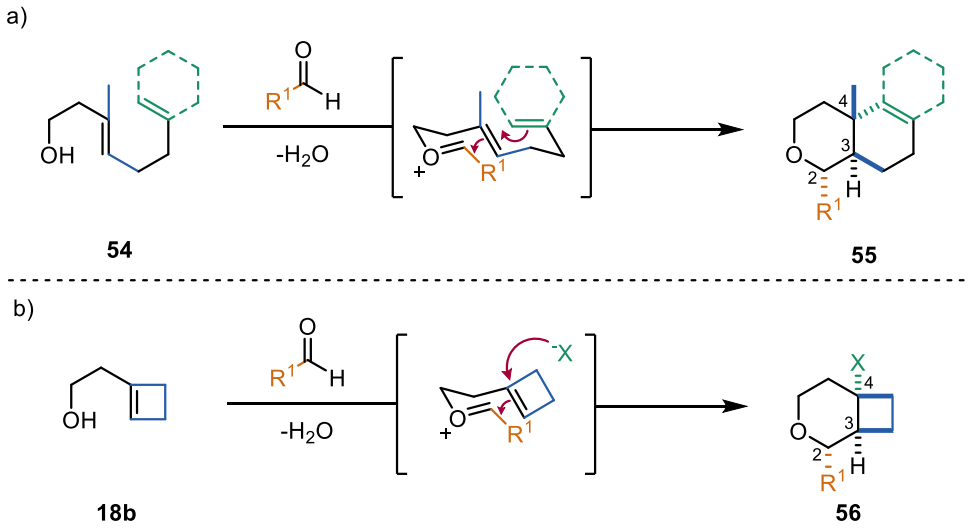
Scheme 39 – Stereochemical outcome in the formation of a) 2,4,6-substituted THPs[108–111] and b) 2,3,4-substituted THPs[112]

Synthesis of 2,3,4,4-tetrasubstituted THPs are even less frequently reported. One rare example from Perron-Sierra *et al.* where good diastereoselectivity was achieved is shown in Scheme 40.[113] In this case, an anomeric effect is proposed to be present in the transition state for carbon-carbon bond formation, and the major product is the one in which groups at the 2,3,4-positions are on one face **53**, with nucleophilic addition of chloride from the opposite face.



Scheme 40 – Anomeric effect in the Prins cyclisation of trisubstituted olefins[113]

Another example, reported by Loh *et al.* outlines a novel synthesis of 3-oxaterpenoids achieved through a Prins-polyene cascade cyclisation (Scheme 41a).[50] The reaction gives fused, multi-substituted THP products in good yields and excellent diastereoselectivities. In this reaction, the *trans*-geometry of the alkene **54** is conserved, leading to the *trans*-relationship between the 3-H and 4-Me in the product **55**. The R^1-group is oriented in a pseudo-equatorial position in the transition state, leading to the *cis*-relationship between 2-R^1 and 3-H of **55**. Comparing this to the Prins cyclisation of cyclobutenes, the same relative stereochemical outcome could be envisaged using a similar rationale (Scheme 41b).

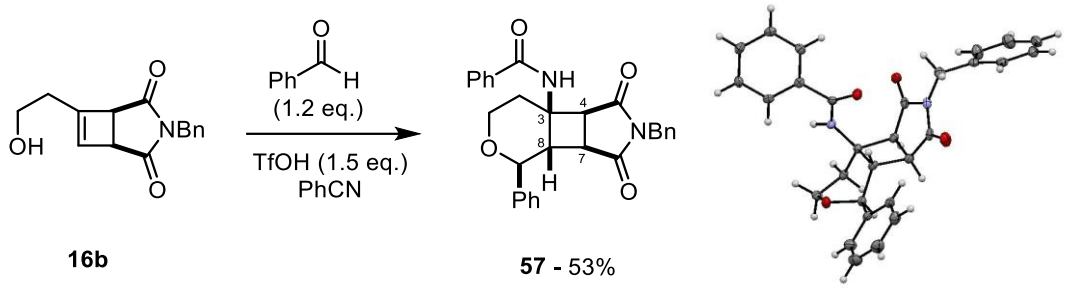


Scheme 41 – Stereochemical outcome of a Prins-polyene cascade[50] and comparison to the cyclobutene system

In a similar manner, it could be envisaged that cyclisation of **18b** would also lead to a *cis*-relationship between 2-R_1 and 3-H in the cyclised product **56**. Intermolecular addition of a nucleophile would be expected to occur such that the *cis*-fused product **56** forms. Despite comparison to similar literature, the Prins cyclisation of cyclobutenes is sufficiently different that prediction of the stereochemical outcome of this reaction was still challenging. Prins reactions with influence from a cyclobutene ring have not been previously reported.

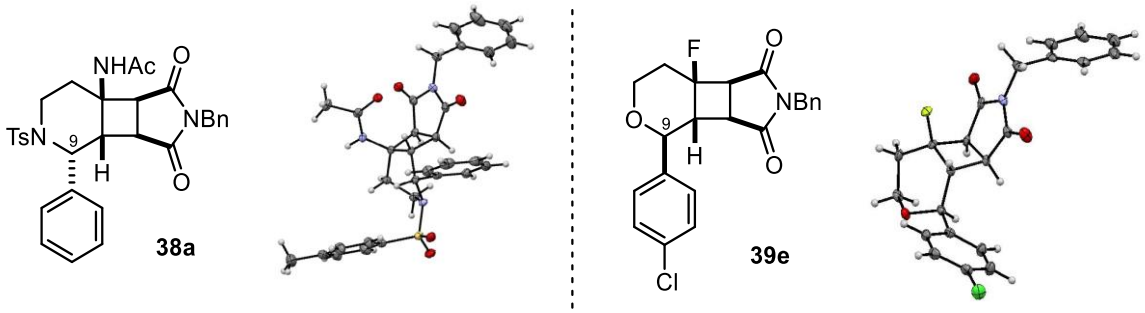
In the Prins-Ritter reactions of **16b** (Scheme 29), it was found that in almost all cases, excellent diastereoselectivity was obtained. In the few examples where the selectivity was lower, the aldehydes used had small substituents that would not bias selectivity in the transition state to such a great extent. Coupling constants and NOE-NMR data for the protons at the C-4, 7 and 8-positions did not give a clear indication of the relative stereochemistry so X-ray crystal structures were obtained to confirm the structure of the isolated diastereomer. This was done through a modification of the original Prins–Ritter reaction to introduce an additional aromatic group and therefore increase crystallinity.

Reaction of **16b** and benzaldehyde in benzonitrile rather than acetonitrile gave the benzamide heterocycle **57** as a crystalline solid in good yield (Scheme 42). The X-ray crystal structure of **57** showed the *cis-anti-cis*-stereochemistry around the cyclobutene, as well as the relative position of the phenyl group incorporated by the aldehyde and this was used to infer stereochemistry for the other cyclobutene Prins-Ritter products in the substrate scope. The relative stereochemistry obtained here matches that obtained in the Prins-polyene cascade example.[50]



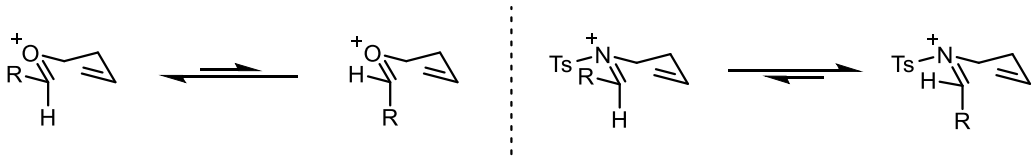
Scheme 42 – Prins–Ritter reaction of cyclobutene **16b** in benzonitrile and crystal structure of **57**

X-ray structures of aza-Prins-Ritter product **38a** and fluoride-Prins product **39e** were also obtained, highlighting an interesting difference in the stereochemical outcome. Fluoride **39e** showed the same stereochemistry as determined for **57**, however the diastereomer formed in aza-Prins reactions **38a** was found to have the opposite stereochemistry at C-9 (Scheme 43).



Scheme 43 – X-ray crystal structures of **38a** and **39e**

This change in stereochemistry can be attributed to the steric bulk of the *N*-tosyl protecting group and has been previously noted for aza-Prins cyclisations.[103] In oxo-Prins reaction, the intermediate responsible for the final stereochemistry adopts a chair-like transition state with all pendent groups occupying equatorial positions if possible. Conversely for aza-Prins reaction, steric clash of the *N*-tosyl protecting group with neighbouring substituent forces this group into an axial position (Scheme 44).

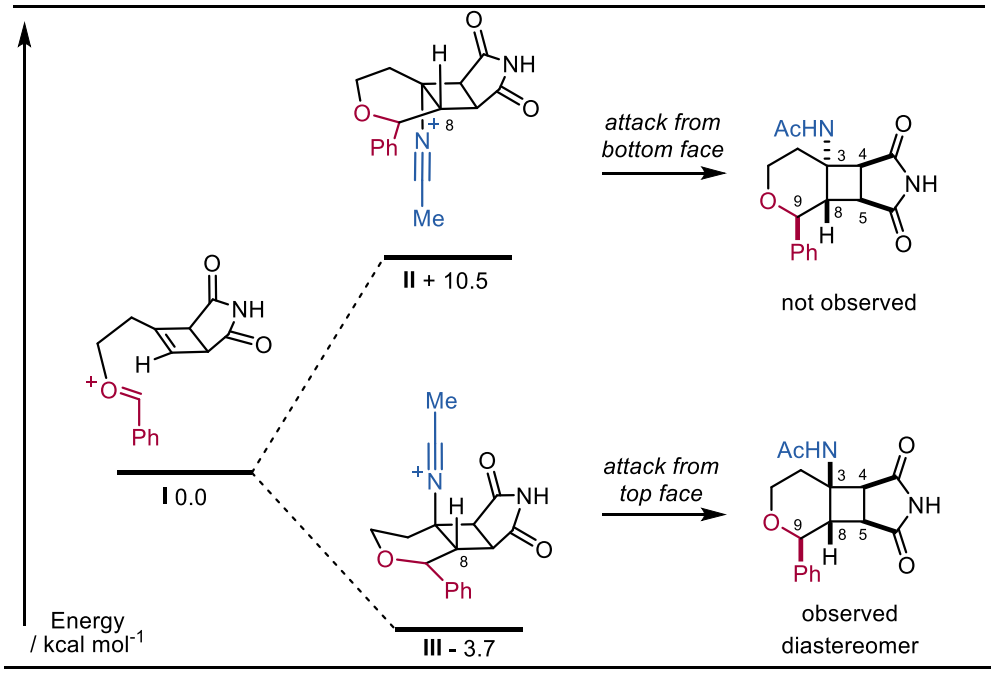


Scheme 44 – Difference in stereoselectivity between oxo- and aza-Prins reactions due to TS interactions

2.3.7. Computational Modelling

DFT modelling was used to rationalise the diastereoselectivity in the Prins reactions. Selectivity at C-9 is well understood and has been discussed in Section 2.3.6, however the reaction creates products with good stereocontrol at all positions. The relative stereochemistry of C-4 and C-7 is set during the [2+2]-photocycloaddition reaction, where exclusively the *cis*-fused product is formed due to the small ring size. This leaves the C-3 and C-8 positions, which are controlled by the transition states of the Prins cyclisation, and computational efforts to determine the control over these stereocentres is described below.

Using DFT, discrete intermediates in the reaction pathway for the Prins cyclisation were optimised to their minimum on the potential energy surface (PES) (B3LYP/6-31+G(d), Gaussian09). Gas phase potential and free energies were considered for each intermediate and gas-phase potential energies relative to the oxocarbenium intermediate **I** are shown in Scheme 45 (Raw data can be found in Section 4.5.1).



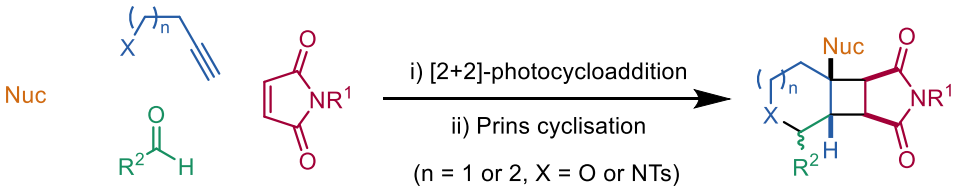
Scheme 45 – Results of DFT calculations showing relative differences in minimised energies for intermediates in the reaction

It was clear from the calculations that the lowest energy conformation of the starting material (in the gas-phase) involves the oxocarbenium of **I** positioning itself on the opposite face of the cyclobutene to the maleimide, presumably to avoid unfavourable steric interactions.

Cyclisation of the alkene from this face would result in the observed relative stereochemistry at the C-8 position. Following this, the resulting carbocation intermediate with the observed C-8 stereochemistry was optimised using the same computational method. No minimum energy corresponding to the tertiary carbocation intermediate could be found, indicating that this could be a transition state structure. It also indicates that cyclisation and nucleophilic attack may be occurring in a more concerted fashion than expected. The intermediates **II** and **III** were optimised, resulting from attack of acetonitrile from either face of the molecule. Gas-phase potential energies for these structures were compared to the oxocarbenium ion showing that the intermediate with the observed stereochemistry at C-3 is *ca.* 14 kcal mol^{-1} lower in energy than the unobserved diastereomer. The results obtained using gas-phase potential energies were then corroborated by the gas-phase free energies and by considering solvation (acetonitrile). All results indicated a preference for the observed stereochemistry. Attempts to locate transition states for the cyclisation pathway were unsuccessful.

2.4. Conclusions

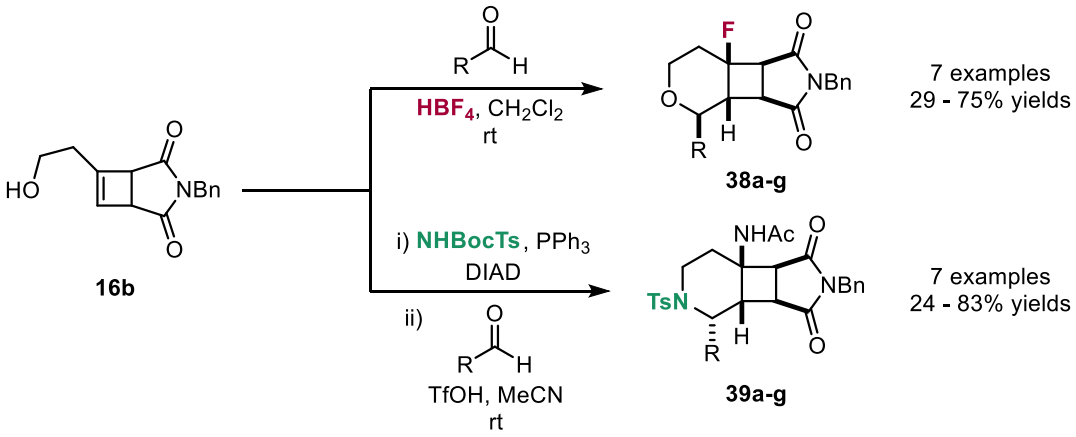
Prins-Ritter reactions of cyclobutene alcohols with aldehydes produced substituted tricyclic scaffolds with excellent stereocontrol and only two modular steps. The products from this reaction are, in most cases, isolated as a single diastereomer, with five contiguous stereocentres (Scheme 46).



Scheme 46 – Diastereoselective synthesis of tricyclic scaffolds from four simple building blocks

The stereochemistry of the products was determined by NOE NMR analysis and X-ray crystallography. The diastereoselectivity of the reaction was excellent in most cases, and only aldehydes with small R^2-groups gave a mixture of diastereomers. Products from the aza-Prins reaction were found exhibit different diastereoselectivity at C-9 due to the bulky nature of the amine protecting group.

Computational modelling of intermediates in the reaction pathway has provided insight and confirmation of the selectivity achieved in these reactions. Energy minimisations for intermediates in the pathway allowed the orientation for the cyclisation and nucleophilic addition steps of the mechanism to be rationalised, giving further understanding of the diastereoselectivity. Transition states for the reaction pathway were not investigated here.

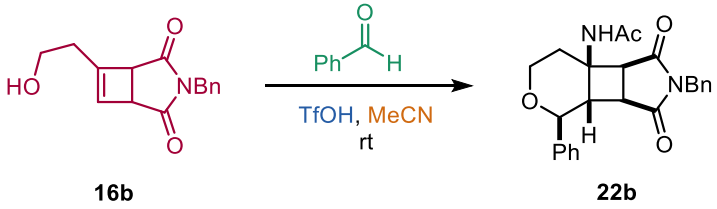


Scheme 47 – Variations on the Prins cyclisation of cyclobutene **16b** incorporating fluoride to form **38a-g** or via Mitsunobu reaction to form **39a-g**

Several variations of the reaction have also been successfully developed and include methods for the synthesis of cyclobutane-fused piperidine products **38a-g**, and 4-fluoro substituted THPs **39a-g** by varying the starting material and nucleophile components of the reaction respectively (Scheme 47). The scope of the reaction has been extensively and successfully explored for all variations by use of a wide range of aldehydes.

Optimisation of the reaction has involved the isolation and characterisation of side products, and methods for preventing the formation of these have been found. Dimeric product **27** was found to be a key by-product which upon column chromatography or similar mildly acidic conditions can degrade to give a 1:1 mixture of **23** and **24**. Formation of the dimer was successfully found to be suppressed simply by a change in the order of addition.

Table 7 – Summary of conditions obtained from optimisation in the reaction of **16b** to give **22b**



	A - benzaldehyde / equiv.	B - triflic acid excess / equiv.	C - addition rate of 16b / equiv. min^{-1}	yield 22b (%)
OVAT	1.20	0.30	-	49
Design 1	1.20	0.10	0.04/0.80	76/73
Design 2	1.02	0.00	0.04/0.80	69/79

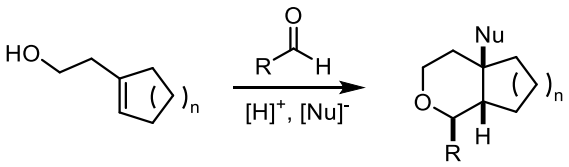
Following this discovery, Design of Experiments was successfully employed and allowed optimisation of the product yield from 49% to 79% relative to optimisation using an OVAT approach (Table 7). Changes in the conditions involved reduction in both the equivalents of benzaldehyde and triflic acid from 1.2 and 1.5 to 1.02 and 1.02 respectively. Addition rate of the starting material was found to have little effect on the yield of **22b**. These statistical results

also gave insight into interactions present between factors, however these were not found to have a significant impact on the outcome of the reaction.

The success of this body of work led to its publication in *Angewandte Chemie – International Edition* in 2019 (See Appendix for full publication).[114]

2.5. Future Work

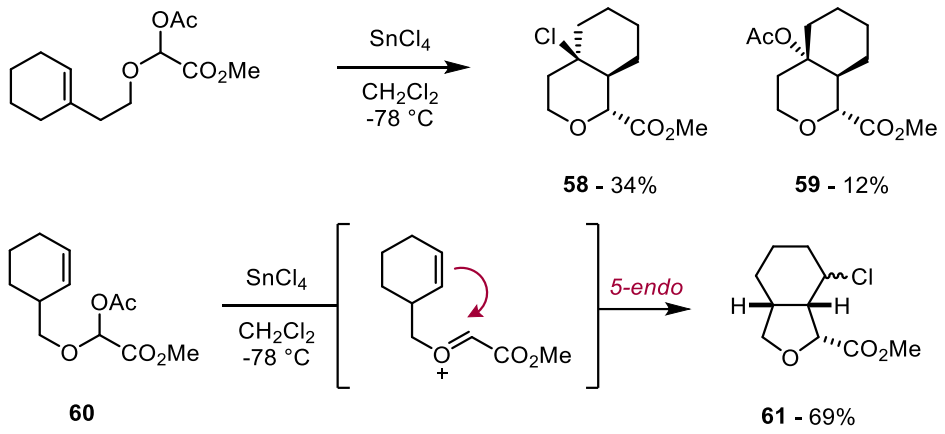
As the reaction of cyclic alkenes in Prins cyclisations has been underexplored, future work in this area should aim to extend the scope of the Prins cyclisation to include such substrates. This may lead to efficient methods for the synthesis of fused tetrahydropyrans, with novel substitution patterns. Influence of fused rings of differing sizes on the resulting stereochemical outcome would also be interesting to investigate (Scheme 48).



Scheme 48 – Proposed extension of the Prins cyclisation for the synthesis of fused tetrahydropyran systems

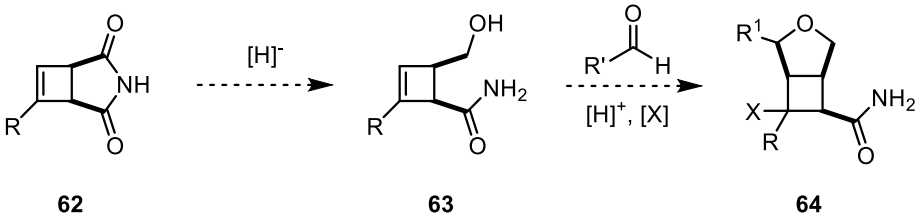
Reaction of 5-membered cyclic olefins for the formation of fused-THPs appears absent from the literature in much the same way as the 4-membered ring systems. Extension of this methodology to cyclopentanes could allow for the facile synthesis of highly substituted fused ring systems.

Cyclohexene Prins cyclisations have also been rarely reported, however a similar π-cyclisation of α-methoxycarbonyl oxycarbenium ions was reported in 1994 by Lolkema *et al.* (Scheme 49)[115] In these reactions it was demonstrated that such substrates could form oxycarbenium ions, analogous to intermediates commonly formed in Prins cyclisations, which undergo similar reactions to form THP systems. Reaction of cyclic olefins under these conditions led to the fused THP products **58** and **59** in moderate yields and selectivity. Interestingly it was also found that reaction of cyclic olefin **60** led instead to the *5-exo* product **61** in good yield.



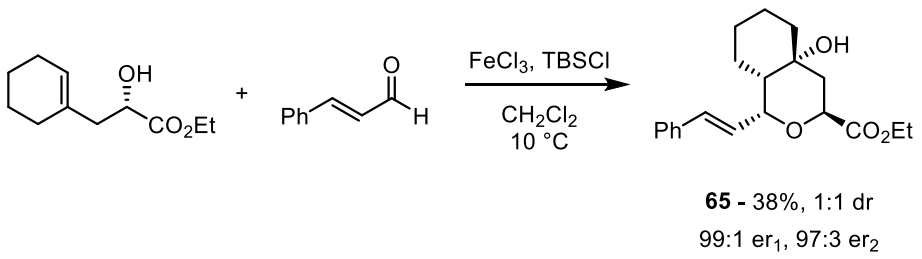
Scheme 49 – Cyclisation of α-methocycarbonyl oxycarbenium ions[115]

Application of this interesting result to the cyclobutene system could be easily achieved through reduction of the maleimide starting material. Unpublished work has shown that maleimides **62** can be regioselectively ring opened and reduced to give products of the type **63** (Scheme 50). Following this, reaction of the resulting cyclobutene alcohol **63** under Prins reaction conditions could lead to the *5-endo* cyclisation as observed in similar literature examples.[115] This could lead to THF-fused cyclobutanes **64** with novel substitution patterns.



Scheme 50 – Application of 5-*exo* cyclisation to cyclobutene alcohols **63**

Another rare example of cyclohexene Prins reactions appears in a substrate scope for a $FeCl_3$ catalysed synthesis of 4-OH tetrahydropyrans reported in 2012 (Scheme 51).[116] In this example the use of cyclic olefins is not the sole focus of the research and as such, the stereochemical result obtained in this example is not extensively explored. The yield and diastereoselectivity for the reaction to form fused-THP **65** are both low.

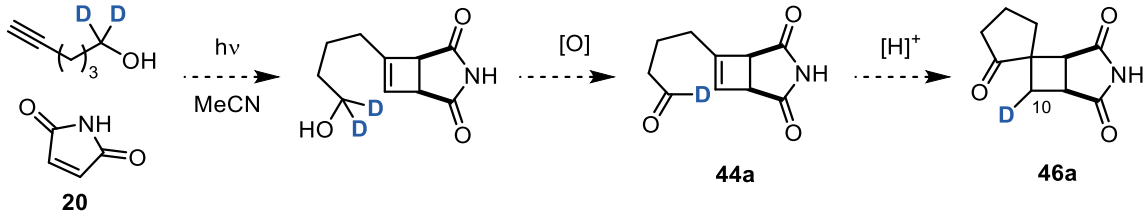


Scheme 51 – Prins cyclisation for the synthesis of cyclohexane-fused THP products[116]

The under-explored area of the Prins cyclisation of cyclic olefins warrants further research into the area. Future work could provide methods for the synthesis of novel fused heterocyclic

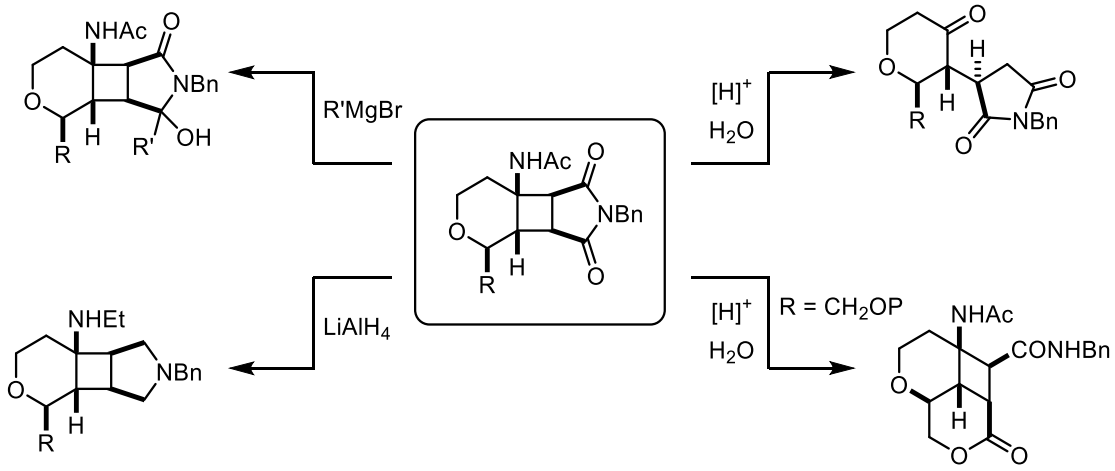
structures of value in the synthesis of natural products as well as use in small molecule scaffolds for medicinal chemistry.

Further development of the alternative reactions outlined in sections 2.3.5.4 and 2.3.5.5 should also be undertaken. Reaction of alcohol **43** under acidic conditions resulted in unexpected and as yet unexplained formation of spirocycle **46.** To elucidate the mechanism for its formation, deuterated aldehyde **44a** and its transformation to deuterated spirocycle **46a** could be investigated (Scheme 52). Extension of the cyclobutene Prins cyclisation methodology to include formation of oxepanes **48** was discussed in Section 2.3.5.5 and also requires further work. Optimisation of the reaction conditions has been carried out however there is still room for improvement and exploration of the substrate scope should be completed.



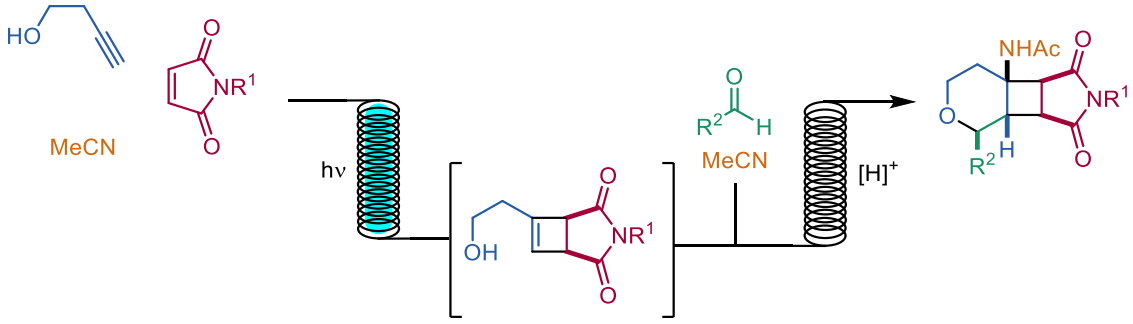
Scheme 52 – Proposed deuterium labelling study to investigate the mechanism for formation of spirocycle **46a**

Although the reaction outlined in this chapter allows successful synthesis of tricyclic scaffolds, their use as scaffolds in medicinal chemistry is dependent on the ease with which derivatives can be synthesised. The reaction is modular, demonstrating the ability for multiple variants of the products to be synthesised by using different aldehydes, acids and nucleophiles. Conversely further reaction of the products obtained has been largely underexplored and additional work into the derivatisation of these interesting structures could be carried out. A few examples of future studies are outlined in Scheme 53 and include nucleophilic addition, global reduction, and acid hydrolysis which could lead to the previously observed ring opened product **24** or with a suitable R-group, may provide options for further cyclisations.



Scheme 53 – Opportunities for derivatisation of the tricyclic scaffolds

A future development of this chemistry could involve the elaboration into a flow process and the development of photochemical processes into flow systems has been extensively researched within the Booker-Milburn group.[73,75,78] Both photochemical and Prins reaction steps can be carried out in acetonitrile, which could allow a solution of starting materials to be flowed through a photochemical reactor, followed by addition of acid or passing the reaction mixture over a solid supported acid catalyst to initiate cyclisation. This would allow transformation from three simple starting materials to a single diastereomer complex fused polyheterocycle in a single flow process (Scheme 54).



Scheme 54 – Development of the photochemical and Prins cyclisation steps into a tandem flow process

Chapter 3: Towards the Total Synthesis of Viburspiran

3. Towards the Total Synthesis of Viburspiran

3.1. Introduction to the Maleidrides

Maleidrides are a class of polyketide natural products consisting of medium sized carbocycles with one or more fused cyclic anhydride moieties. The first maleidrides were reported in 1931 by Wijkman,[117] who characterised two compounds, glaucanic and glauconic acid, **66** and **67**, that were isolated from *Penicillium glaucum*, and later the structural isomer byssochlamic acid **68** was isolated by Raistrick (Figure 16).[118] These three maleidrides were biosynthesised from C_9 precursors, leading to their naming as 'nonadrides'. The term is now more widely used to describe maleidrides consisting of a nine-membered carbocyclic core such as scytalidin **69**,[119] deoxyscytalidin **70** and cornexistin **71**,[120] and analogous octadride (viburspiran **72** and zopfiellin **73**)[121] and heptadride (agnestadride A, **74**),[122] natural products have since been isolated.[123]

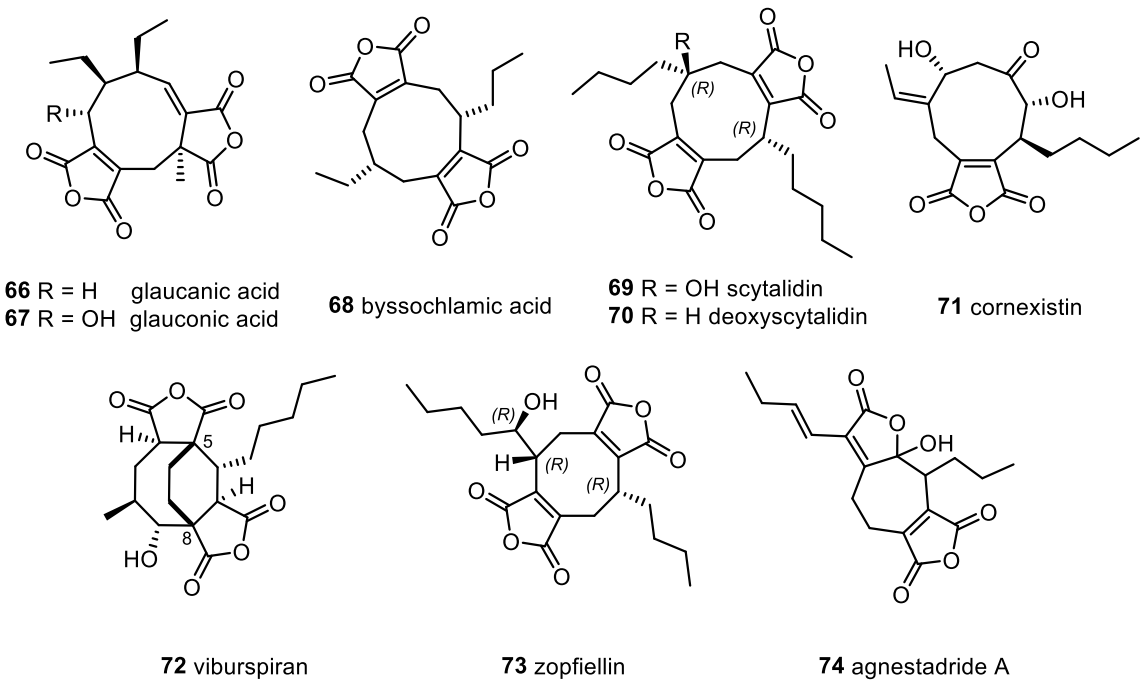
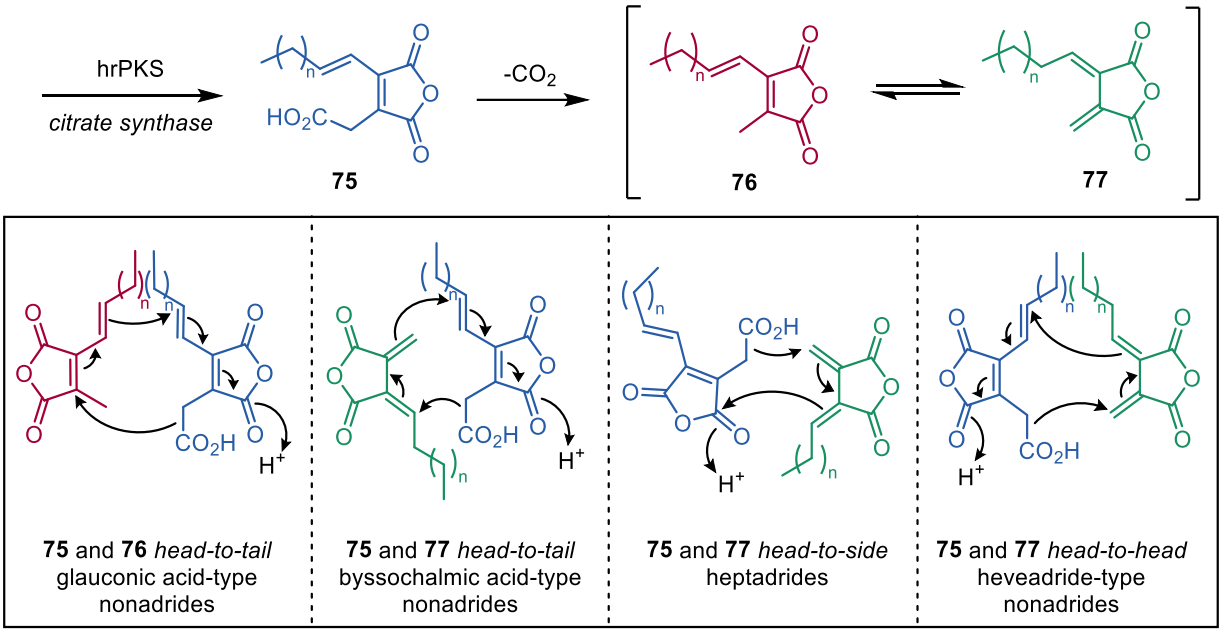


Figure 16 – Natural products in the maleidride family

Viburspiran **72** and zopfiellin **73** are both octadrides with an eight-membered carbocyclic framework. Both contain two cyclic anhydride units, however viburspiran has an additional ethylene bridge from C-5 to C-8 giving each a quaternary centre and therefore a structurally interesting and challenging target for total synthesis.

The biosynthesis of maleidrides has been studied extensively[124–128] and the use of isotopic labelling, gene knockouts and heterologous expression experiments has allowed the formulation of a universal pathway towards the maleidrides[125] based on dimerisation of maleic anhydride monomers. Monomers **75**, **76** and **77** are formed via an iterative highly reducing polyketide

synthase (PKS) followed by coupling of the PKS product with oxaloacetate by citrate synthase-like enzymes then subsequent dehydration (Scheme 55, **75**), decarboxylation (Scheme 55, **76**) and tautomerisation (Scheme 55, **77**). Coupling of two of these monomers can then occur, with different dimerisation orientations leading to different general maleidride structures (Scheme 55).



Scheme 55 – Proposed general pathway to maleidride natural products[125]

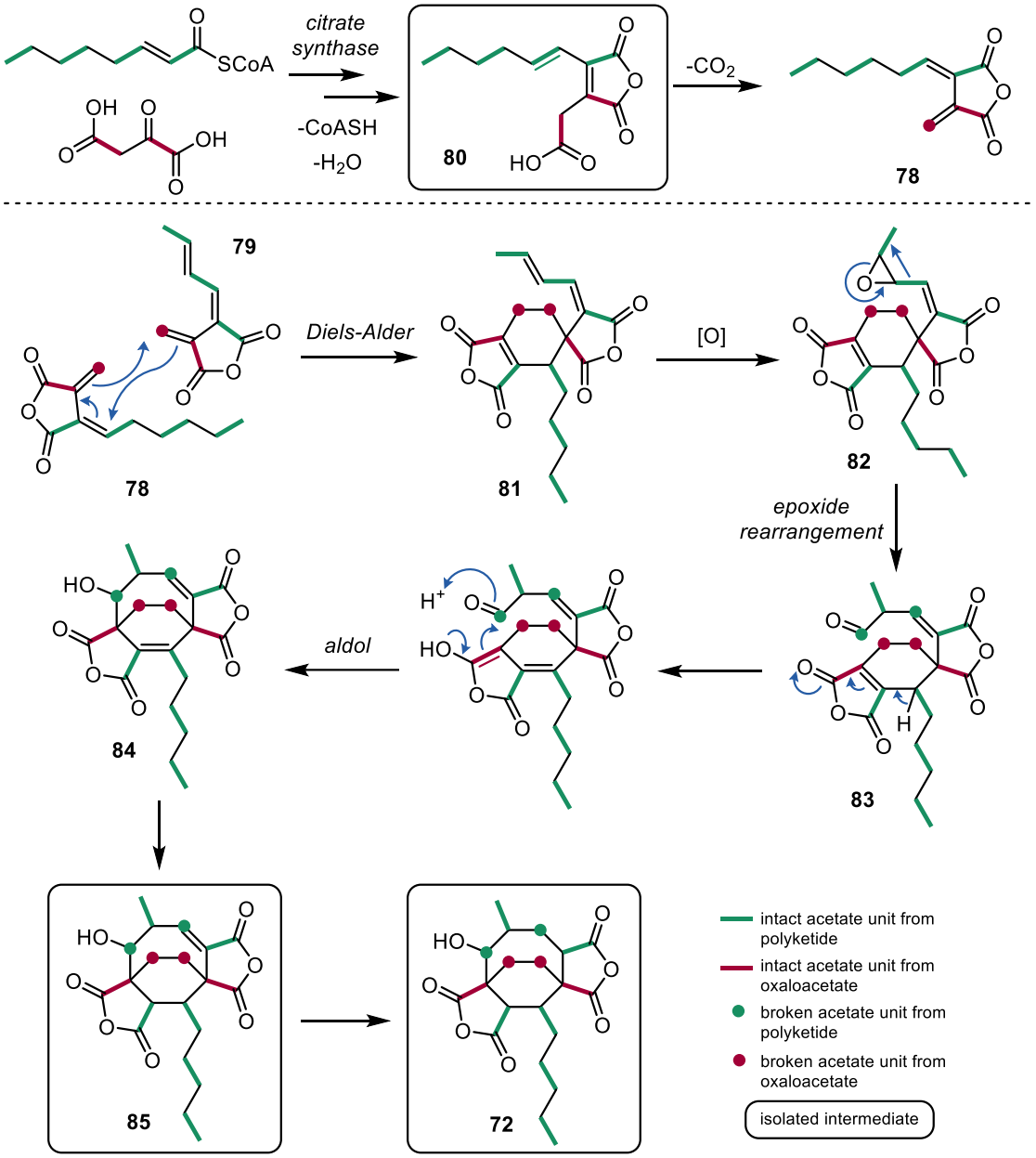
In 2020, Willis *et al.* confirmed the absolute stereochemistry of both zopfiellin **73** and scytalidin **69** using X-ray crystallography along with evidence from the biosynthetic pathway.[128–130] Synthesis of a *p*-nitrobenzoate derivative of **73** and Mosher's ester derivatives allowed determination of its absolute stereochemistry. The discovery that the biosynthesis of both zopfiellin **73** and scytalidin **69** occurs through the common intermediate deoxyscytalidin **70** allowed the absolute stereochemistry of **69** and **70** to be inferred.[127,128]

3.1.1. Viburspiran

Viburspiran **72** was isolated in 2011 from the fungal endophyte *Cryptosporiopsis sp.,* and its structure and absolute stereochemistry determined by NMR analysis, X-ray crystallography and circular dichroism (CD) calculations. **72** exhibits antifungal activity against the fungi *Microbotryum violaceum* and *Botrytis cinerea*, however no antibacterial activity was observed against the strains tested.[121]

Biosynthetic work carried out by C. Greco provided insight into the biosynthetic pathway responsible for the formation of viburspiran.[131] Feeding studies with [^{13}C]-labelled precursors showed that viburspiran is constructed from the tetraketide monomer **78** and a triketide monomer **79**, which is thought to arise from a series of oxidations and rearrangements of **80**

(Scheme 56). A proposed head-to-head dimerisation of **78** and **79** forms hexadride **81**. This is then oxidised to epoxide **82** which can undergo a Meinwald rearrangement[132] to give **83**, the presence of which was confirmed by results from ^{13}C-labelling studies. Intramolecular aldol reaction forms **84** which can then undergo a series of alkene reductions, confirmed by isolation of **85**, to give viburspiran **72**. Although work has been carried out on its biosynthesis, to date there has been no published total synthesis of viburspiran.

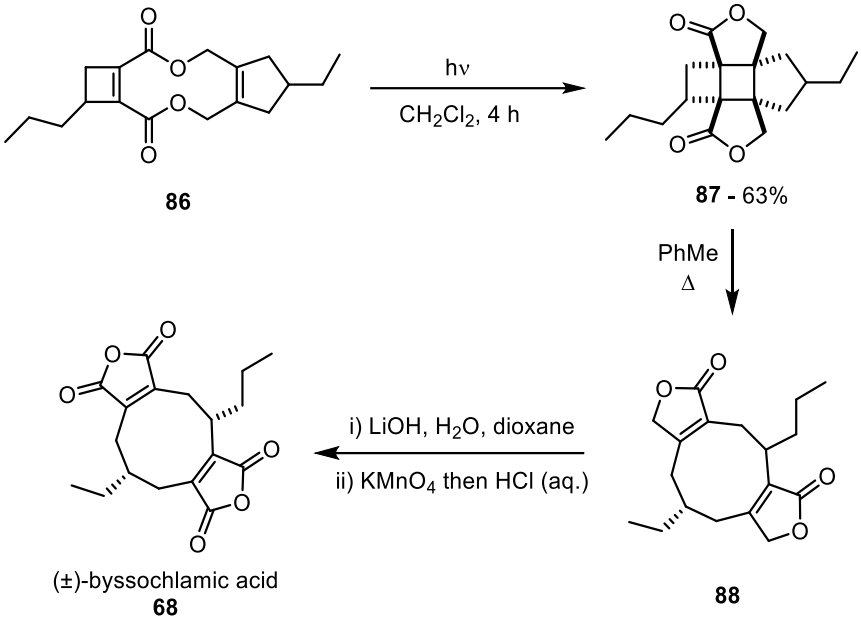


Scheme 56 – Proposed biosynthetic pathway for the formation of viburspiran based on ^{13}C-labelling studies

3.1.2. Photochemistry in the Synthesis of (±)-Byssochlamic Acid

Total synthesis of maleidride natural products has been investigated in the past and the successful total syntheses of byssochlamic acid[133–135] and cornexistin[136,137] have both been completed. Work is ongoing in the Willis research group towards the total syntheses of zopfiellin[130] and scytalidin.[129]

In 1992, White and co-workers reported a total synthesis of (±)-byssochlamic acid **68** using a key photochemical step (Scheme 57).[133] Thereafter an enantioselective synthesis of **68** was described based on the same route.[135]



Scheme 57 – Key photochemical step in the total synthesis of (±)-byssochlamic acid by White *et al.*[133]

The key step in White's synthesis involved a photoaddition-cycloreversion metathesis to form the nine-membered ring system, with pendent lactones that could be later converted to the necessary anhydrides. As well as the key photochemical step, a photochemical [2+2]-cycloaddition was used to synthesise the cyclobutene portion of the substrate **86**. Intramolecular [2+2]-cycloaddition of **86** gave the 4-membered ring product **87** which, upon heating in toluene, underwent cycloreversion to give **88**. Basic hydrolysis followed by oxidation also resulted in epimerisation of the propyl side chain to give solely the more stable and naturally occurring *cis*-product, **68**. White *et al.* revisited the synthesis in 2000 and reported modifications to the route to allow the synthesis of both enantiomers of byssochlamic acid.[135]

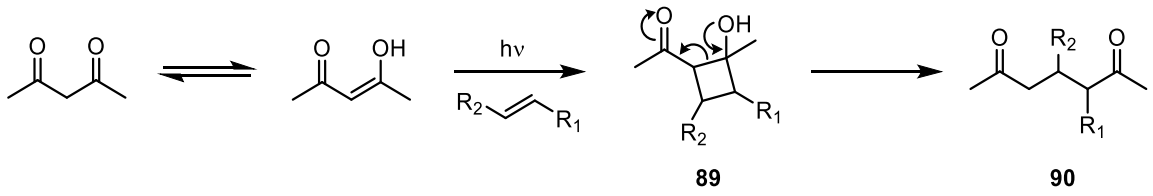
This synthesis showcases the potential for photochemistry in the synthesis of medium ring systems in relatively few steps. The presence of maleic anhydrides in the maleidride natural products also makes them ideal candidates for total synthesis by photochemical routes, due to

the versatility of maleic anhydrides, maleimides and diacids/diesters as chromophores in photochemistry.[133,135]

3.1.3. Ring-Opening of Cyclobutanes and the de Mayo Reaction

[2+2]-Photocycloaddition is one of the most efficient methods for the synthesis of cyclobutanes, a structural feature found in many natural products.[138] However cyclobutanes are not only useful for the synthesis of natural products; their inherent ring strain is a property that can be taken advantage of in the formation of larger sized rings through fragmentation. Tandem [2+2]-cycloaddition-fragmentation sequences allow the elegant construction of more complex ring structures. Fragmentation pathways include Grob fragmentation, radical fragmentations, formal metathesis and de Mayo reactions.[7,9] In this report, the de Mayo reaction will be explored as a method for the synthesis of medium-sized ring natural products.

The de Mayo reaction is the combined reaction pathway involving [2+2]-photocycloaddition of an enone (or α,β-unsaturated carbonyl compound) with an alkene, followed by a retro-aldol reaction. It was reported in 1962 by de Mayo and co-workers after the observation of the production of 1,5-diketones from the irradiation of alkenes in the presence of acetylacetone.[139]

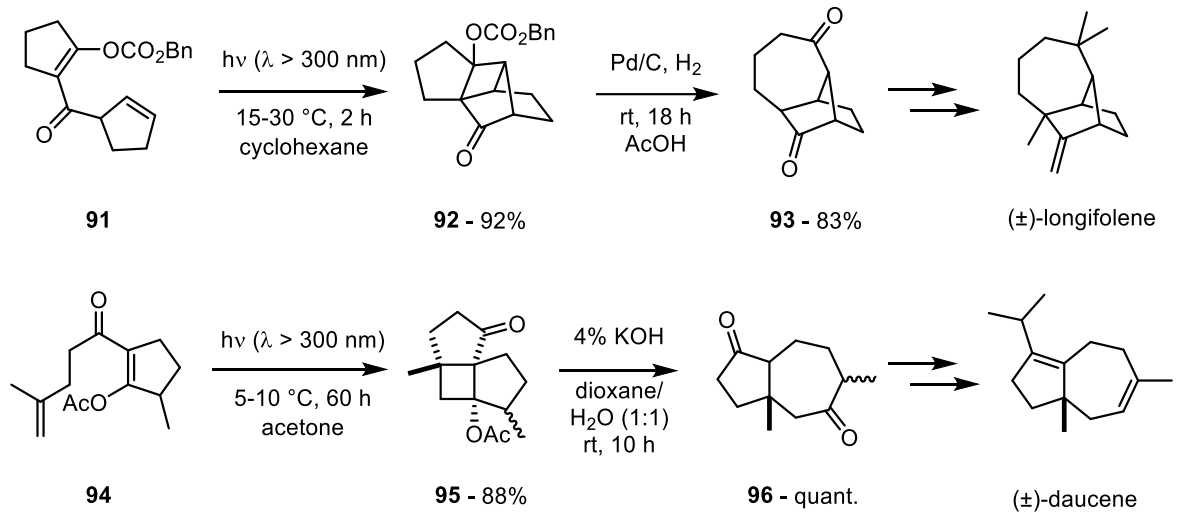


Scheme 58 – de Mayo photocyclisation/retro-aldol reaction[139]

The de Mayo reaction requires the enol tautomer of the 1,3-dicarbonyl compound to act as the chromophore, allowing [2+2]-photocycloaddition with an alkene to occur (Scheme 58). The resulting β-acylcyclobutanol **89** can then spontaneously fragment through a retro-aldol pathway to give a 1,5-diketone **90**. Poor regioselectivity is often obtained in the de Mayo reaction due to the need for the triplet 1,4-biradical to undergo spin inversion to a singlet biradical for the cyclobutane to form, although this can be more easily controlled in intramolecular systems.[15,140]

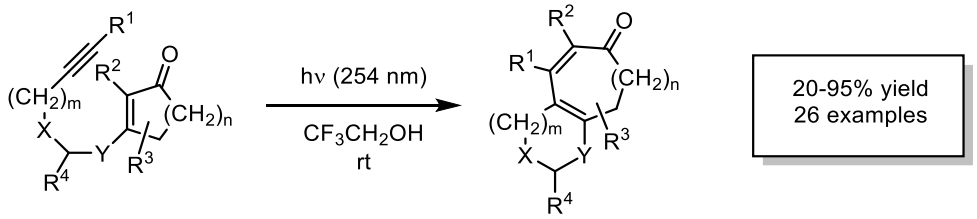
The de Mayo reaction has been used in numerous total syntheses, including (±)-daucene and (±)-longifolene (Scheme 59).[141] Both syntheses involve an intramolecular [2+2]-photocycloaddition of a 1,3-diketone that has been protected as the enol tautomer to assist in photocyclisation. Irradiation allows cyclisation to the cyclobutane. In the synthesis of (±)-longifolene, photocycloaddition of **91** gave the cyclobutane product **92**, then hydrogenation of the benzyl carbonate revealed the alcohol which underwent the retro-aldol step of the de Mayo reaction sequence to form the ring expanded product **93**.[142] For (±)-daucene, irradiation of the key intermediate **94** resulted in regioselective photocyclisation to **95**, followed by alkaline

hydrolysis of the acetate to initiate a retro-aldol reaction to the seven-membered ring **96**.[143] These examples highlight the potential for de Mayo reaction sequences as powerful tools in the synthesis of medium-sized ring-containing natural products.



Scheme 59 – Use of the de Mayo reaction in the total synthesis of (±)-longifolene[142] and (±)-daucene[143]

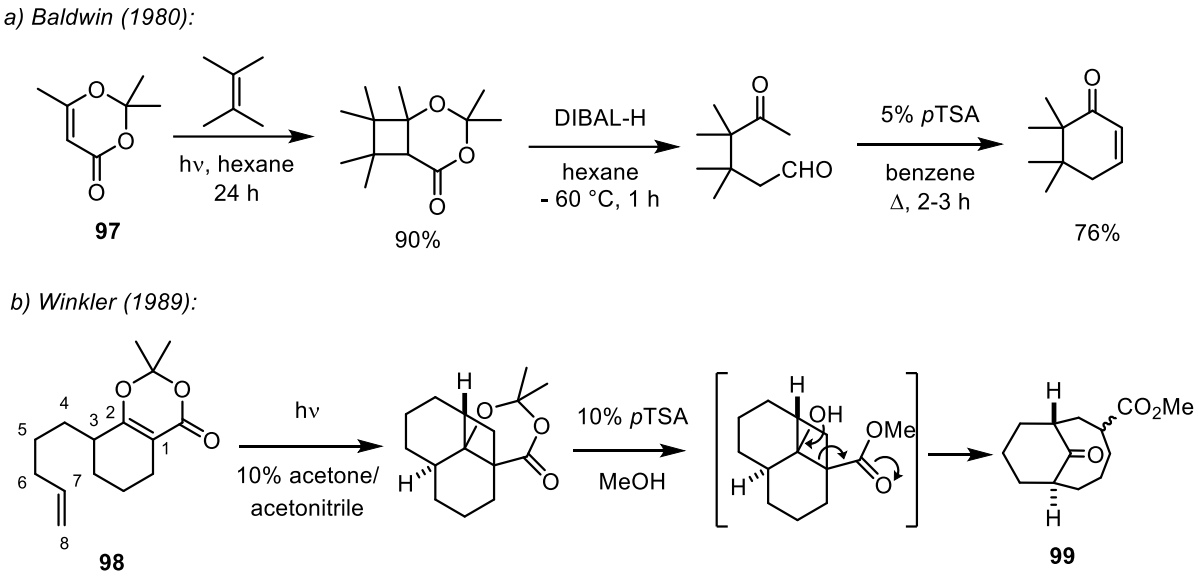
Recent developments of the de Mayo reaction have included a visible light mediated process between 1,3-diketones and α or β-substituted styrenes using a visible light photosensitiser. Seven-membered rings were also shown to be successfully synthesised using this methodology.[144] In another recent publication, medium sized carbocycles have been synthesised through an intramolecular de Mayo reaction with alkyne tethers (Scheme 60). The scope of the reaction is broad in terms of chain lengths and heteroatoms, giving access to a range of substituted medium ring structures.[145]



Scheme 60 – Recently reported alkyne de Mayo reaction to give substituted medium-sized carbocycles[145]

Although the de Mayo reaction has been repeatedly applied to 1,3-diketones, extension to β-keto esters has not been as successful since β-keto esters are reluctant partners in [2+2]-photocycloadditions because of the ease of their tautomerisation.[146,147] Baldwin reported a solution to this problem in 1980; a variation employing the dioxenones of the β-keto esters, such as **97**, covalently locking the 1,3-dicarbonyl in the enol form (Scheme 61a).[148] This chemistry has been extended by Winkler, who has investigated the intermolecular use of this chemistry on substrates such as **98** to synthesise medium sized rings **99**,[149,150] as well as the stereochemical implications of using dioxenones in [2+2]-photocycloaddition (Scheme 61b).[151–

[153] The methodology has also been applied to several total syntheses[154,155] and used to develop methods for asymmetric [2+2]-photocycloadditions.[156]

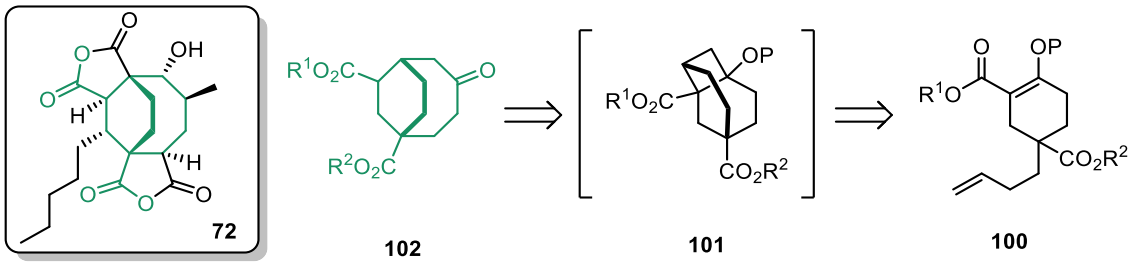


Scheme 61 – Developments in the photochemistry of dioxenones by Baldwin[148] and Winkler[150,153]

3.2. Aims

The broad aim of this project was to utilise photochemical methods in the synthesis of medium-sized ring natural products, namely maleidrides. Ring expansion through a de Mayo reaction was seen to be an ideal route towards the core structure of these natural products. Anhydride functionality around the ring also complements the unsaturated carbonyl functionality necessary for photochemical reactivity.

Viburspiran was chosen as a target due to its interesting, bridged ring system and 8-membered ring core. It was proposed that the core structure could be synthesised through an intramolecular de Mayo cyclisation (Scheme 62).



Scheme 62 – Retrosynthetic plan for the synthesis of the viburspiran core

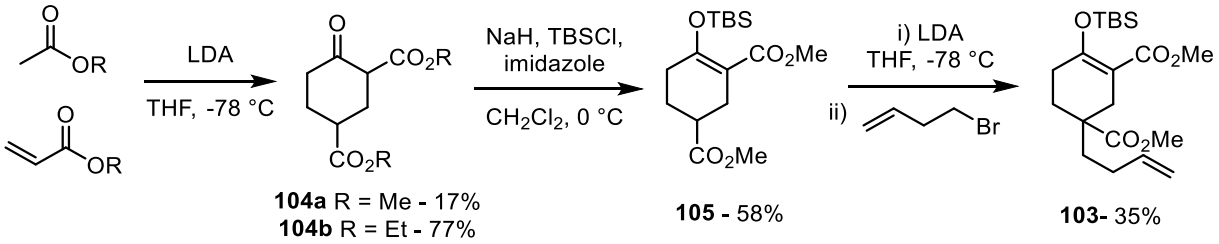
Irradiation of protected β-keto ester with the general structure **100** should give the [2+2]-photoaddition product **101**, which could, upon deprotection, spontaneously ring open in a de Mayo reaction to give the core structure **102** of viburspiran. This would leave two esters in place to later form anhydrides, along with a ketone which could be used to introduce the

methyl and alcohol groups. Initial investigations involved the synthesis of a model substrate to prove the viability of the proposed key step.

3.3. Results and Discussion

3.3.1. Synthesis of the Model Substrate **103**

Investigations into the total synthesis of viburspiran began with the formation of a model substrate that could be used to test the suitability of the key intramolecular photochemical step. Ester **103** was identified as a suitable target, with a TBS-enol ether acting as the chromophore and a butenyl tether to form the bridge (Scheme 63). Synthesis of **103** was achieved in three steps from commercially available starting materials. Michael–Michael–Dieckmann cyclisation of methyl acetate with methyl acrylate following a literature procedure gave diester **104a**.[157,158] The yield for this step was initially lower than quoted in the literature but was later found to be more successful using ethyl acetate and ethyl acrylate to give **104b**. Silyl protection of the β-ketoester gave **105**, and was followed by alkylation to give the target substrate **103**.



Scheme 63 – Synthesis of a model substrate for intramolecular photocycloaddition

UV-Vis analysis of the model substrate **103** confirmed that the absorption was in an appropriate region for photochemical excitation (Figure 17). However irradiation of **103** in acetonitrile with a 125 W medium pressure Hg lamp returned only starting material. The reaction was repeated with the thioxanthone photosensitiser ITX but again, only starting material was obtained. It was thought this could be due to the bulky nature of the TBS protecting group blocking access to the enol alkene. It has also been noted previously in the literature that β-ketoesters are notoriously poor partners in [2+2]-photocycloaddition reactions, even when protected as the silyl enol ethers or enol acetates.[159]

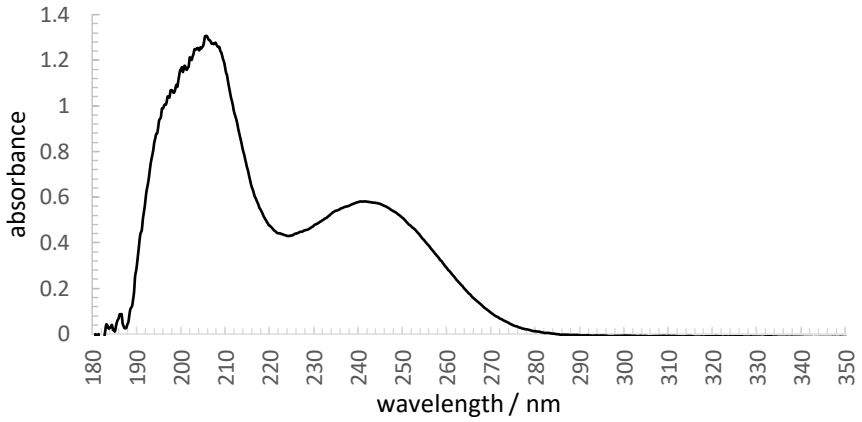


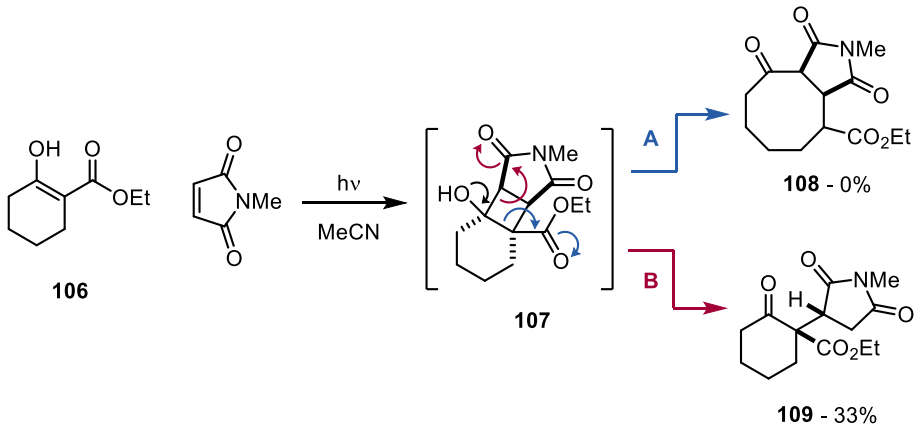
Figure 17 – UV-Vis absorbance of **103**

Based on this result, several alternative chromophores were considered for use in the key-step of the synthesis. In 1980, Baldwin demonstrated that dioxenones can act as surrogates for β-ketoesters in de Mayo reactions, requiring a simple acidic or basic hydrolysis to undergo the ring-opening step.[148] Alternatively, the Booker-Milburn group has extensive experience of the use of maleimides and maleic anhydrides in [2+2]-photocycloadditions.[160–163] Both approaches were investigated as potential solutions for the key-step in this total synthesis.

3.3.1.1. Maleimides as Chromophores in [2+2]-Photocycloadditions

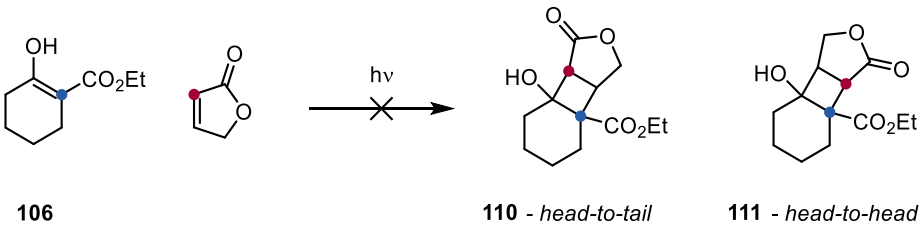
Due to the succinic anhydride units present in viburspiran, it was envisaged that a maleimide or maleic anhydride could be used as a chromophore in a [2+2]-photocycloaddition and incorporate the functionality into the final structure. Maleimide has been found to be a more effective chromophore than maleic anhydride in photochemical reactions and protected maleimides can be easily converted to anhydrides at a later stage in the synthesis.[164,165]

It was envisaged that [2+2]-photocycloaddition of *N*-methylmaleimide with β-ketoester **106** may form the cyclobutane intermediate **107**, which upon fragmentation would give the ring expanded eight-membered ring with a fused maleimide unit, **108** (**A** - Scheme 64). Although **106** did undergo the desired photocycloaddition to **107**, an unexpected fragmentation occurred instead (much like the fragmentation observed as a side product of the Prins cyclisation – Section 2.3.3) to give **109** (**B** - Scheme 64). The second observation of this fragmentation demonstrates the ease with which cyclobutane fused maleimides can fragment in this way.



Scheme 64 – [2+2]-Photocycloaddition of β-ketoesters with maleimides

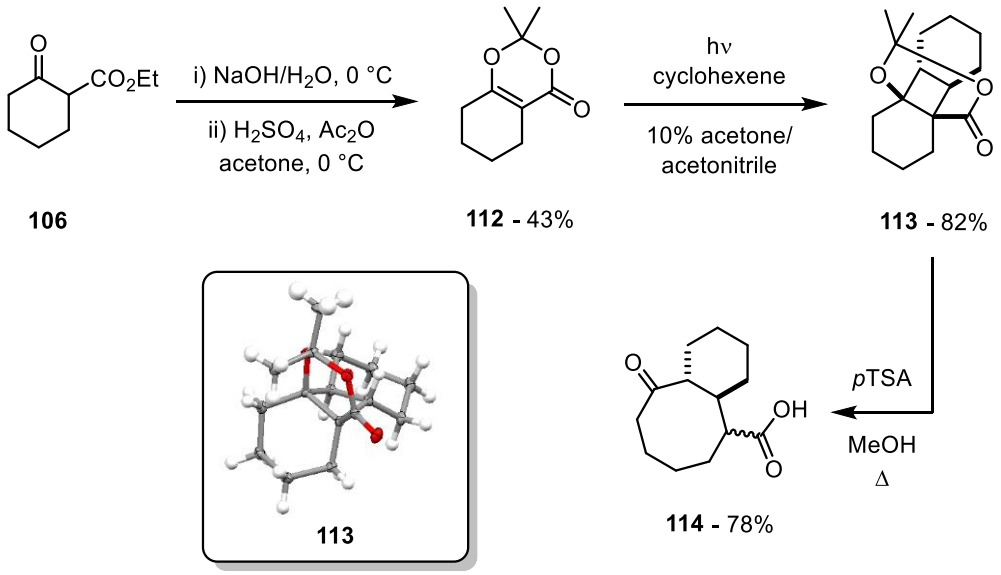
In order to suppress this fragmentation, the carbonyls of the maleimide would need to be removed, however this would also remove the key functionality of the maleimide to act as a chromophore. One possibility would be to replace the maleimide with 2-furanone, which could lead to the two regioisomeric products **110** and **111** (Scheme 65). Literature precedent for the regioselectivity of [2+2]-photocycloadditions suggests that the head-to-head product **111** would be formed preferentially as electron-withdrawing groups usually lead to head-to-head products, (Section 1.4.1).[20] Fragmentation of **111** would lead to the desired eight-membered ring. Unfortunately upon irradiation of **106** with 2-furanone, no reaction was observed.



Scheme 65 – Possible solution to fragmentation problem using 2-furanone

3.3.1.2. Dioxenones as Chromophores in [2+2]-Photocycloadditions

To test the suitability of the dioxenone methodology, an intermolecular model reaction was first carried out. Although this lacks the ethylene bridge in the natural product viburspiran, it was a valuable proof of concept before carrying out further intramolecular substrate synthesis. Dioxenone **112** was synthesised based on a literature procedure from β-ketoester **106** and then irradiated in the presence of cyclohexene in 10% acetone/acetonitrile (acetone acts as a photosensitiser)(Scheme 66).[149,166] This gave the [2+2]-product **113** in 82% yield and 2D-NMR, HRMS and X-ray crystallography were used to confirm the structure of the product. **113** was then subjected to the ring-opening conditions to give the cyclooctane product **114** in 78% yield.

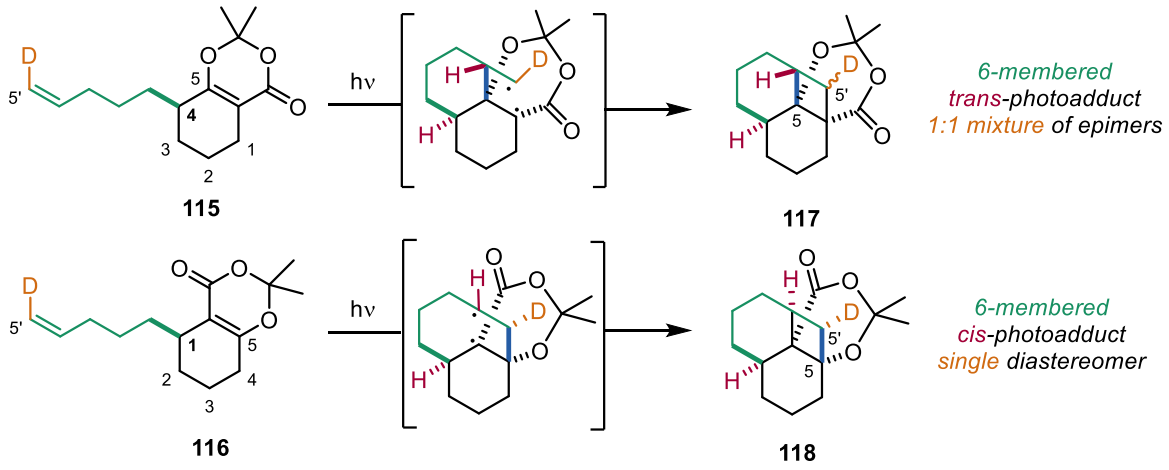


Scheme 66 – Intermolecular trial reaction of a dioxenone in the de Mayo reaction

With the success of the intermolecular reaction of dioxenone **112** and cyclohexene, efforts turned towards synthesis of an analogous intramolecular system, with the hope of using this method to synthesise the carbocyclic core of viburspiran.

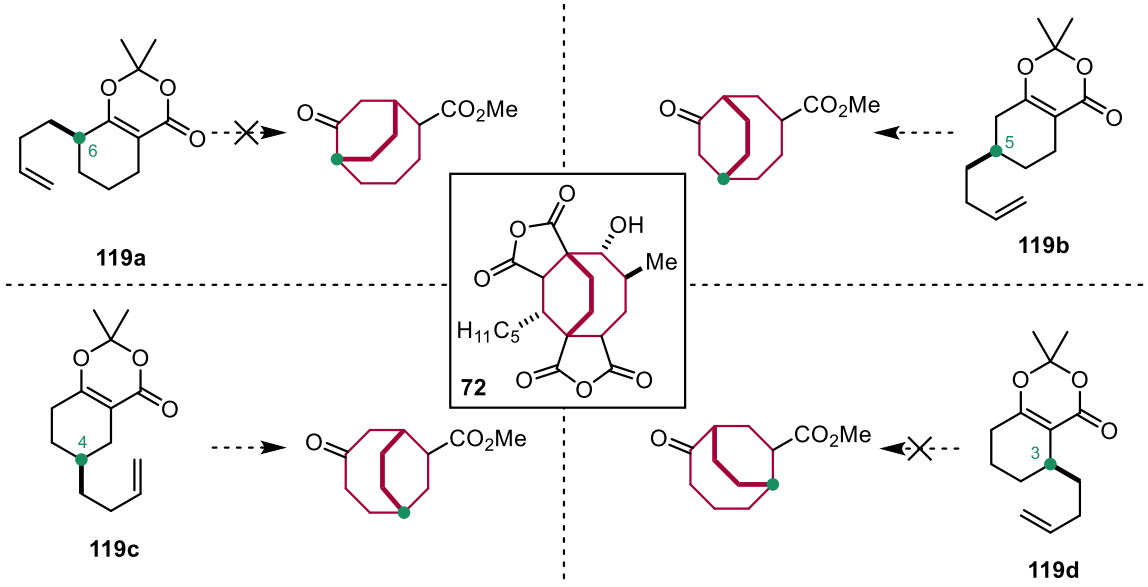
3.3.2. Intramolecular Dioxenone Substitution Patterns

In 1989 Winkler *et al.* explored the effect of the substitution-position of dioxenones (or dioxenone transposition) on the stereochemical outcome of [2+2]-cyclisation in intramolecular dioxenone reactions (Scheme 67).[152] Two dioxenones **115** and **116** were subjected to UV-light and both cyclised to give the straight cycloaddition products, as would be predicted based on the relative rate of formation of possible ring sizes. Their relative stereochemistry differed however, with **115** and **116** forming the *trans*- and *cis*-photoadducts respectively. Deuterium labelling was used to explain this difference, **117** was isolated as a 1:1 mixture of epimers, whereas **118** was a single diastereomer at the C-5' position. This indicates that upon excitation, formation of a bond with C-5 of the dioxenone occurs first, allowing conformation relaxation of the resulting biradical prior to intersystem crossing. For **117** this allows epimerisation at the C-5' position and explains formation of a 1:1 mixture of diastereomers, and for **118** this allows formation of the more stable *cis*-photoadduct.



Scheme 67 – Effects of dioxenone transposition on the stereochemistry of intramolecular [2+2]-cycloadditions[152]

To form the core structure of viburspiran, a similar intramolecular dioxenone approach was proposed, using a tether one methylene unit shorter than the substrates investigated by Winkler.[152] Various substitutions **119a-d** were considered and predictions on their suitability made based on the previous literature and the rate of formation for the intermediate biradical species (Scheme 68). As the rate of formation of a cyclopentylmethyl biradical is around 75 times faster than that for the cyclohexyl biradical, 5-membered rings are often preferentially formed, a rule often referred to as the 'rule-of-five'.[26,29] The rule is a useful predictive tool, and in this case would predict that, given **119a** and **119d** are able to form 5- or 6-membered rings through straight or crossed cycloadditions, the 5-membered ring would predominate and they would therefore not form the required carbocycle. For **119b** and **119c**, the cycloaddition would proceed to form either 6- or 7-membered rings, in which case formation of the 6-membered ring would be kinetically favourable. Therefore, substitution at C-4 or C-5 may mean that **119c** and **119b** respectively are more suitable for the synthesis of the desired carbocyclic core.

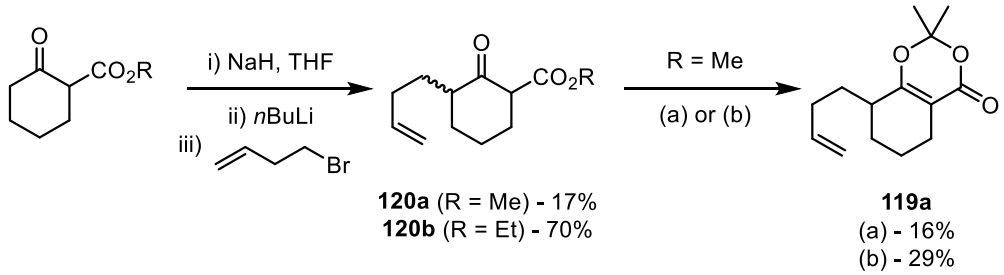


Scheme 68 – Predicted suitability for substitution patterns leading to a viburspiran-type core

To investigate the selectivity of the variously substituted dioxenones **119a-d**, these model substrates were synthesised. Routes to the four intramolecular substrates **119a-d** were based on the original method published by Winkler,[150] as well as using well known Michael-addition chemistry.

3.3.2.1. Synthesis of 6-butenyldioxenone **119a**

Synthesis of 6-butenyldioxenone **119a** proceeded through dianion alkylation of **106** to give **120** in 70% yield, followed by dioxenone formation (Scheme 69).[149] Several methods for the synthesis of dioxenones from β-ketoesters have been reported by Sato and Winkler.[167,168] The method described by Sato involves the basic hydrolysis of the β-keto ester, followed by reaction with acetone in the presence of acetic anhydride and catalytic sulfuric acid. Although this method was successful in the synthesis of **119a**, the yield was only 16% over the two steps, possibly due to the instability of the intermediate β-ketoacid which is prone to decarboxylation(Scheme 69).



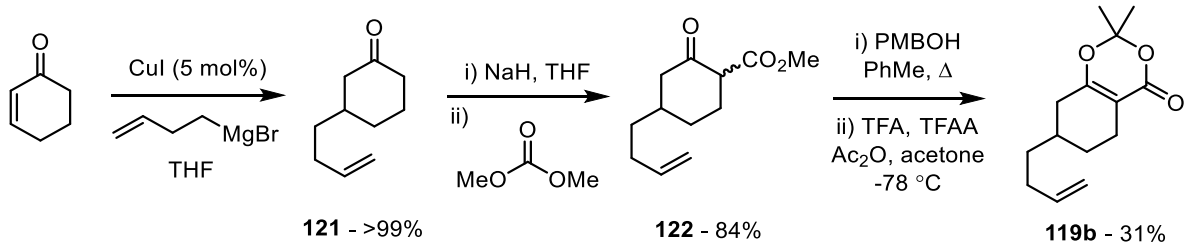
Scheme 69 – Synthesis of 6-butenyldioxenone **119a.**

(a) i) NaOH, H_2O ii) H_2SO_4, Ac_2O, acetone (16% over 2 steps) (b) i) PMBOH, *p*TSA, toluene, Δ (73%) ii) TFA, TFAA, Ac_2O, acetone (40%)

A more commonly used method involves using a *t*-butyl or *p*-methoxybenzyl β-ketoester as a precursor to dioxenones.[151,152,154,168,169] These can be reacted with acetone in the presence of an excess of trifluoroacetic acid and trifluoroacetic anhydride to form the desired dioxenone in high yields. In this case, transesterification proceeded smoothly in a 73% yield, however in the formation of **119a** from **120**, only a 40% yield was achieved (literature reactions using the same conditions have been achieved in 80% yield[151]). Along with this low yield, the product was found to be inseparable from other *p*-methoxybenzyl related side products. Neither of the methods here resulted in formation of **119a** with a comparable yield to the literature and further work could be carried out to optimise this transformation by investigating both the reaction conditions and product purification procedures.

3.3.2.2. Synthesis of 5-butenyldioxenone **119b**

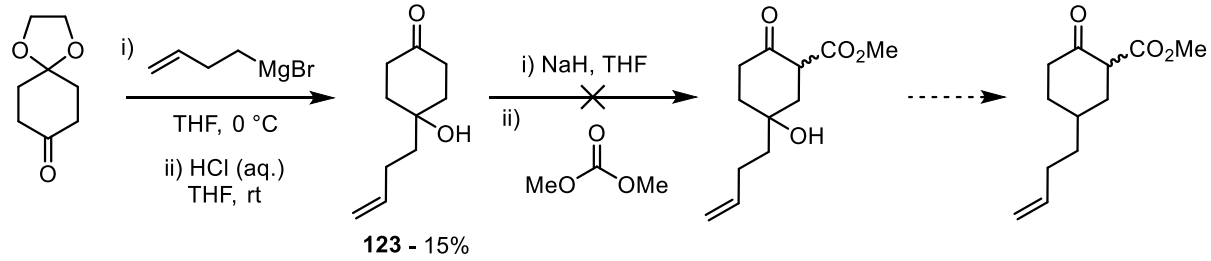
Synthesis of the 5-butenyldioxenone **119b** was carried out through conjugate addition of 3-butenylmagnesium bromide with cyclohexenone giving **121** (Scheme 70). Deprotonation of **121** followed by reaction with dimethylcarbonate gave exclusively ester **122** substituted at the least-hindered position, as has been previously observed with similar reactions.[170] Pleasingly, optimisation of the reaction conditions allowed for high yields (99% and 84%) to be achieved for both of these steps. In a similar manner to the previous dioxenones, **119b** was synthesised by transesterification with *p*-methoxybenzyl alcohol followed by acid-mediated formation of the dioxenone to give the 5-butenyldioxenone **119b**.



Scheme 70 – Synthesis of 4-butenyldioxenone **119b**

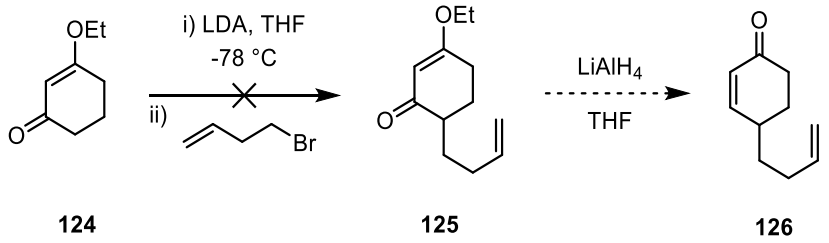
3.3.2.3. Synthesis of 4-butenyldioxenone **119c**

The first method investigated for the synthesis of **119c** was through Grignard addition to a mono-protected 1,4-cyclohexanedione, followed by methoxycarbonylation with dimethyl carbonate (Scheme 71). It was then envisaged that Barton radical deoxygenation could be used to remove the tertiary alcohol if necessary.[171] Although Grignard addition gave alcohol **123**, the yield (15%) was low and attempts at methoxycarbonylation were unsuccessful, presumably due to the presence of the tertiary alcohol. Therefore, an alternative method for the synthesis of **119c** was devised.



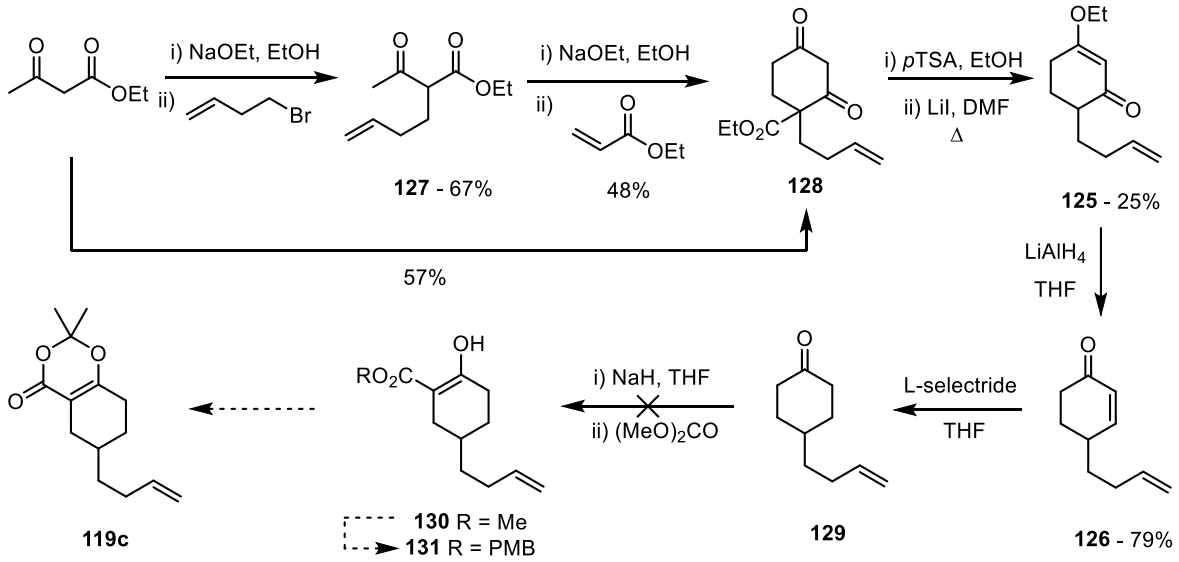
Scheme 71 – Attempted synthesis of **119c**

The new approach involved alkylation of enol ether **124** to give **125,** which could be subsequently reduced to give enone **126** (Scheme 72). This Stork-Danheiser enone transposition has been previously reported as a method for the synthesis of functionalised cyclohexenones.[172] Despite several attempts at this reaction, alkylation to form **125** was unsuccessful and only unreacted starting material was returned.



Scheme 72 – Alkylation followed by Stork-Danheiser enone transposition to give enone **126**

A final alternative route to **119c** (Scheme 73) was devised involving a cyclisation reaction similar to that used in the synthesis of initial model substrate **103** (Scheme 63). Ethyl acetoacetate was alkylated to give the substituted β-ketoester **127**, which then underwent further alkylation with ethyl acrylate and spontaneous cyclisation to give **128**. It was also found that this sequence could be carried out in one-pot without a detrimental impact on the yield. **128** bears an ester in the 4-position which needed to be removed. A direct Krapcho decarboxylation of **128** gave no reaction, however decarboxylation was successful when carried out after formation of the ethyl enol ether and gave **125** in 25% yield over the two steps.



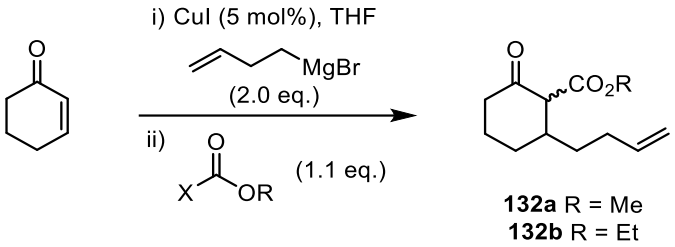
Scheme 73 – Current route towards 4-substituted dioxenone **119c**

Enone transposition of **125** with lithium aluminium hydride gave **126** in 79% yield, which was then reduced with L-selectride® to give ketone **129.** Ketone **129** was found to be slightly volatile and was carried through to the subsequent step immediately. Unfortunately, the attempted carbonylation was unsuccessful and, due to time constraints, the synthesis of **119c** was not completed.

3.3.2.4. Synthesis of 3-butenyldioxenone **119d**

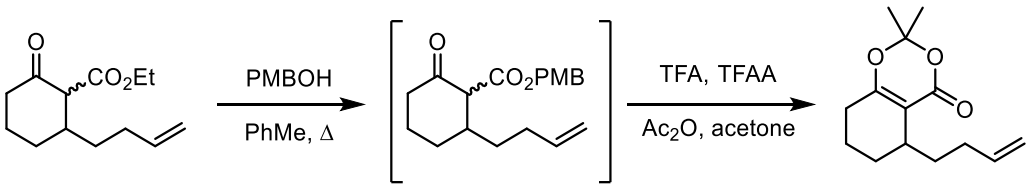
Synthesis of 3-butenyldioxenone **119d** was achieved through conjugate addition of a butenylorganocuprate, followed by addition of methyl chloroformate. Although successful in the formation of the β-ketoester **132** (Table 8), the yield for this reaction was poor (14%) so alternative conditions were investigated.

Table 8 – Optimisation of the synthesis of **132**



entry	X	R	yield of **132a/b** (%)
1	Cl	Me	14
2	OMe	Me	0
3	im	Me	45
4	CN	Et	69

As alternatives to the chloroformate, dimethyl carbonate, *N*-(carbomethoxy)-imidazole (Heller-Sarpong reagent, Entry 3, Table 8) and methyl cyanoformate (Manders' reagent) were investigated (Table 8). Dimethylcarbonate returned only starting material. The Heller-Sarpong reagent was originally developed for the mild esterification of carboxylic acids but has also been shown by Herzon *et al.,*[173] to be successful in a similar conjugate addition – acylation reaction.[174] It was used in this case to give the β-keto ester **132a** in 45% yield, however it was not as successful as the cyanoformate which gave the ester **132b** in 69% yield. As the reaction was being carried out on a small-scale, formation of cyanide was not a problem, however if this reaction were to be later incorporated into a larger scale synthesis, the Heller-Sarpong reagent has the advantage of avoiding the production of cyanide waste, as well as being a cheaper alternative.



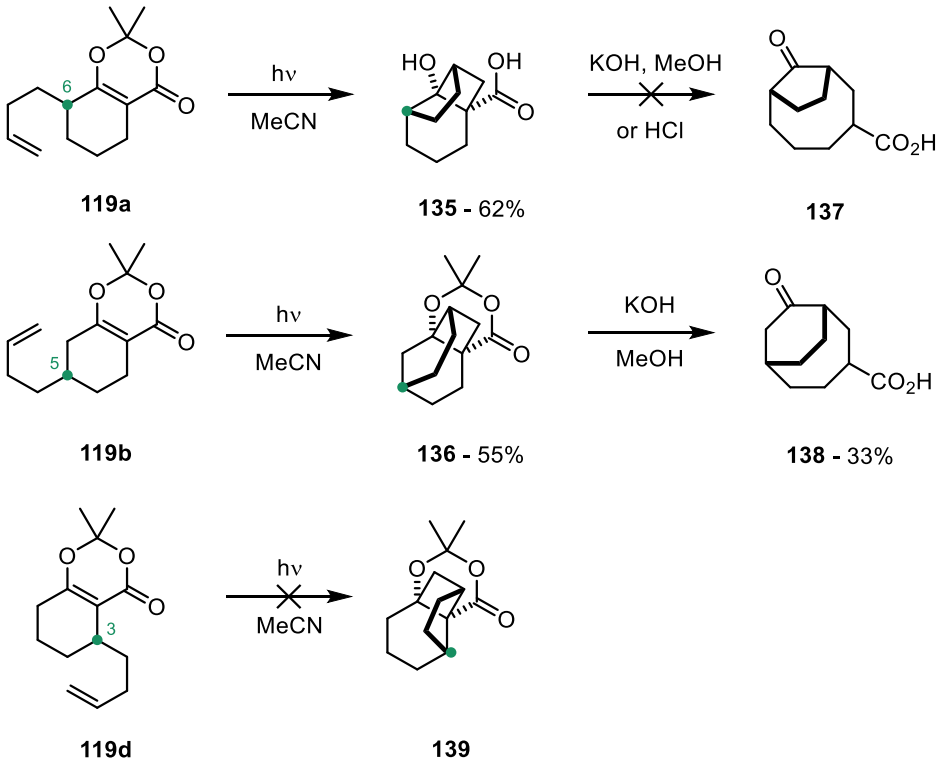
133 **134** **119d** - 37%

Scheme 74 – Synthesis of the 3-butenyldioxenone **119d**

Once the synthesis of **133** had been achieved, the final steps to form the dioxenone were carried out (Scheme 74). Transesterification with *p*-methoxybenzyl alcohol gave **134** which was directly converted to dioxenone **119d** with TFA, TFAA, Ac_2O and acetone in 37% yield over two steps. As previously observed, a small amount of *p*-methoxybenzyl containing side product was present in the final product.

3.3.3. [2+2]-Cycloaddition to form the Carbocyclic Structure of Viburspiran

With **119a**, **119b** and **119d** successfully synthesised, the [2+2]-photocycloaddition and ring opening reactions were carried out (Scheme 75). Each substrate was subjected to UV-light from a medium pressure mercury lamp. Pleasingly **119a** and **119b** both underwent cycloaddition reactions to give **135** and **136** respectively. As previously predicted, irradiation of **119a** gave the 5-membered product as is often favoured in radical reactions. The structure of **135** was confirmed by ADEQUATE-NMR which provides correlations of carbon and proton chemical shifts through successive J_{CH} and J_{CC} couplings. In this example correlations between C-1 and H-3 and between C-2 and H-4 (Figure 18) provided confirmation that the 5-membered ring product had been formed. **135** was unexpectedly isolated as the free carboxylic acid rather than the protected product which could have been a result of impurities present in the starting material due to the challenging purification of precursors. Under both acidic or basic hydrolysis conditions, no conversion to the ring-opened product **137** was observed.



Scheme 75 – Cycloaddition and fragmentation reactions of the model substrates **119a, 119b** and **119d**

119b gave the cyclised product **136** when subjected to the same photochemical conditions, in this case with the dioxenone still intact. The structure of **136** was again confirmed by ADEQUATE-NMR showing correlations between C-1 and H-3 and between C-2 and H-4 (Figure 19). Under basic conditions **136** was hydrolysed and spontaneously ring opened to give **138**, matching the core carbocyclic structure of viburspiran.

Unfortunately, when **119d** was subjected to the photochemical conditions, no cycloaddition product **139** was observed and only starting material was returned. The reason for this was unclear but suggested substitution at the 6-position as unsuitable for the synthesis of the viburspiran core.

These investigations revealed that the substitution pattern in **119b** was suitable for the synthesis of the core viburspiran scaffold. Despite the difficulties in synthesis of model substrate **119c**, the possibility of using this substitution pattern in a total synthesis of viburspiran was not ruled out, as along with **119b**, it is predicted to give the correct core structure on reaction under photochemical conditions.

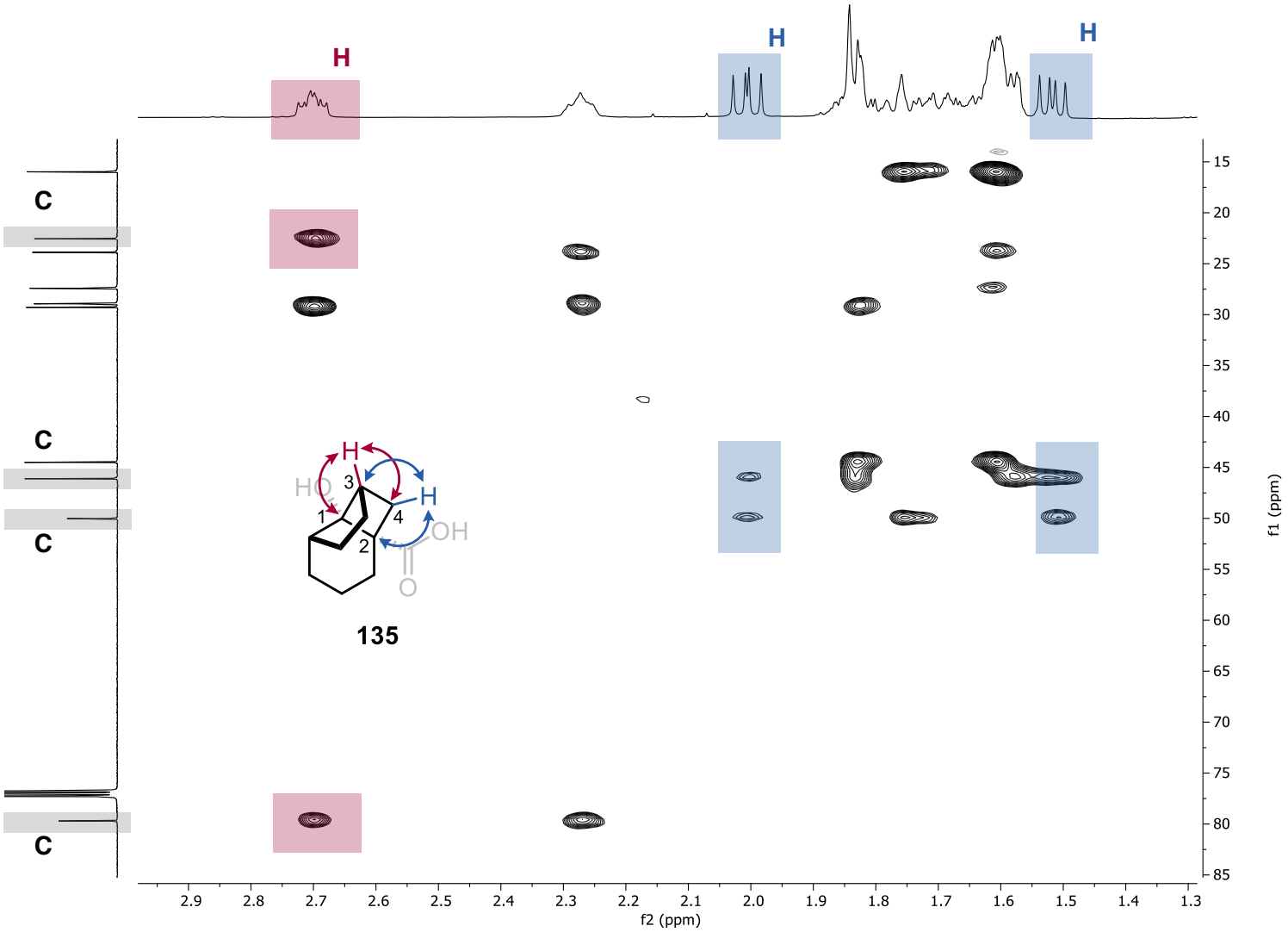


Figure 18 - ADEQUATE-NMR of **135** to confirm regiochemistry, showing correlations between H-3 and C-1 & C-4 and between H-4 and C-2 & C-3

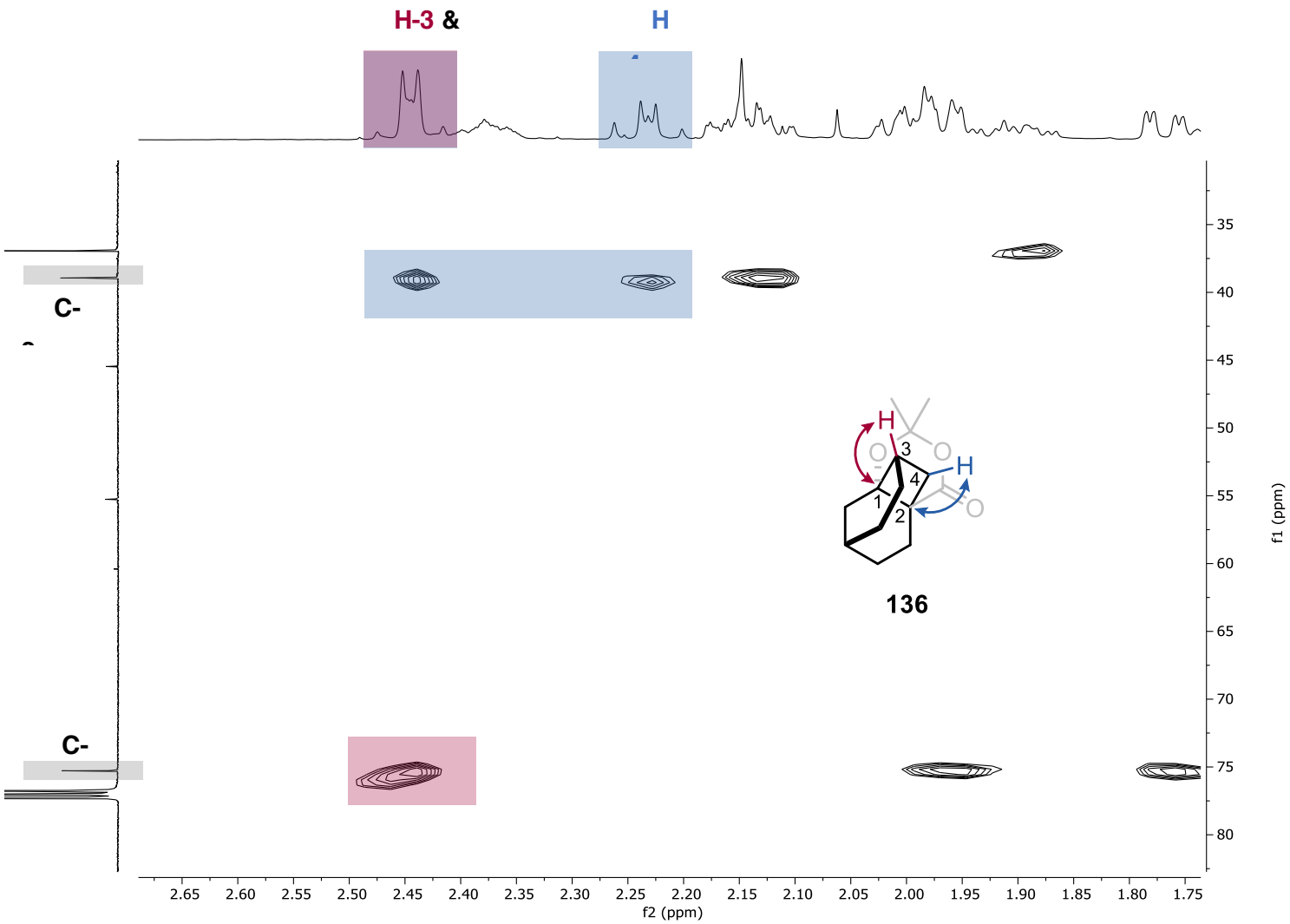
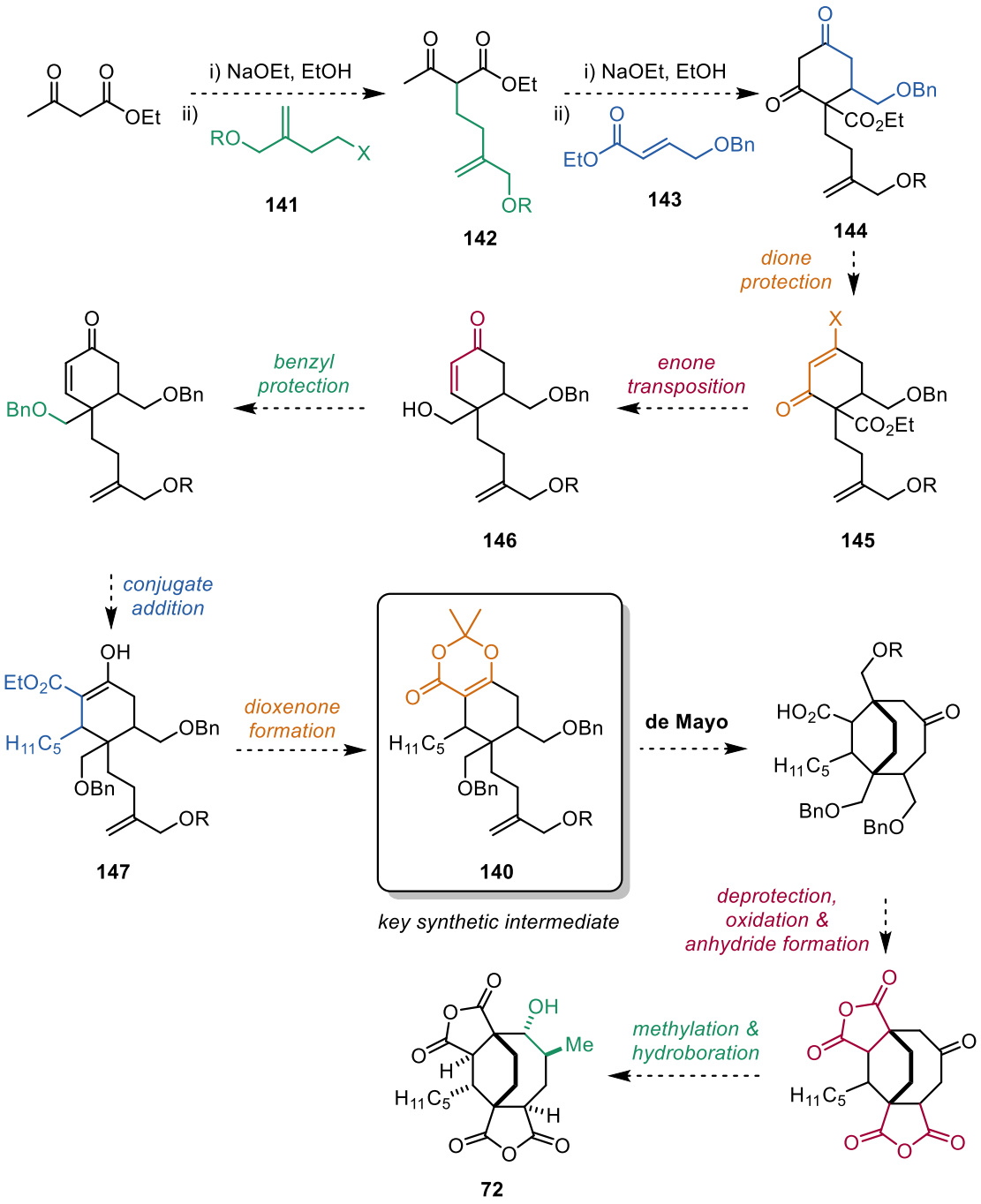


Figure 19 - ADEQUATE-NMR of **136** to confirm regiochemistry, showing correlations between H-3 and C-2 & C-1, and between H-3 and C-1

3.3.4. First Generation Synthetic Route

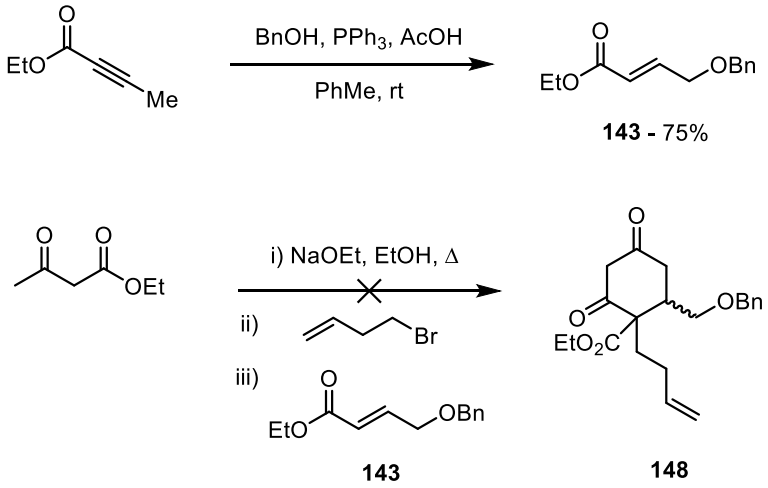
Having demonstrated that the core structure of viburspiran can be synthesised using the [2+2]-photocycloaddition reaction of dioxenones such as **119b** or **119c**, a synthetic route to viburspiran **72** was proposed (Scheme 76). Based on literature procedures, a route with substitution at the 4-position (**119c**) of the dioxenone appeared to provide a wider range of synthetic options than substitution at the 3-position (**119b**). The resulting bicyclo[4.2.2]decane structure provides functional groups in positions that allow for easier late-stage functionalisation to viburspiran.



Scheme 76 – First generation synthesis plan for viburspiran using key dioxenone intermediate **140**

The key target in the synthesis was identified as **140**, in which the 4-butenyldioxenone would also be functionalised with necessary groups to form the anhydrides at a later stage. The decision was made to use benzyl ethers, which could later be removed by hydrogenation, then oxidation and ring closure would give the anhydrides. Benzyl ethers are widely compatible with a range of reaction conditions, including photochemistry, allowing the greatest flexibility throughout the route.

The synthetic route towards **140** was designed such that the majority of required substituents were installed prior to the photochemical step, after which their incorporation would become more challenging (Scheme 76). Alkylation of ethyl acetoacetate with alkylating agent **141** to give **142** would provide a protected alcohol for later conversion to an anhydride as well as the required alkene for photochemistry. Subsequent cyclisation with **143**, using a similar method to that demonstrated in synthesis of model substrates (Scheme 73), would give diketone **144**. As has been previously shown, there is potential for these two reactions to be performed in a one-pot process. Transformation of the ketone to a protected enol or vinyl halide **145** would allow enone transposition to **146** to occur. Conditions for the enone transposition would be likely to also reduce the ester, however this could be easily protected as a third benzyl ether. Conjugate addition of the enone **146** followed by trapping of the electrophile with cyanoformate to give **147** and subsequent formation of the dioxenone would give the key intermediate **140** ready for photochemical cyclisation. Later steps in the synthesis included global deprotection and anhydride formation, and incorporation of the C-2 methyl and C-1 hydroxyl.

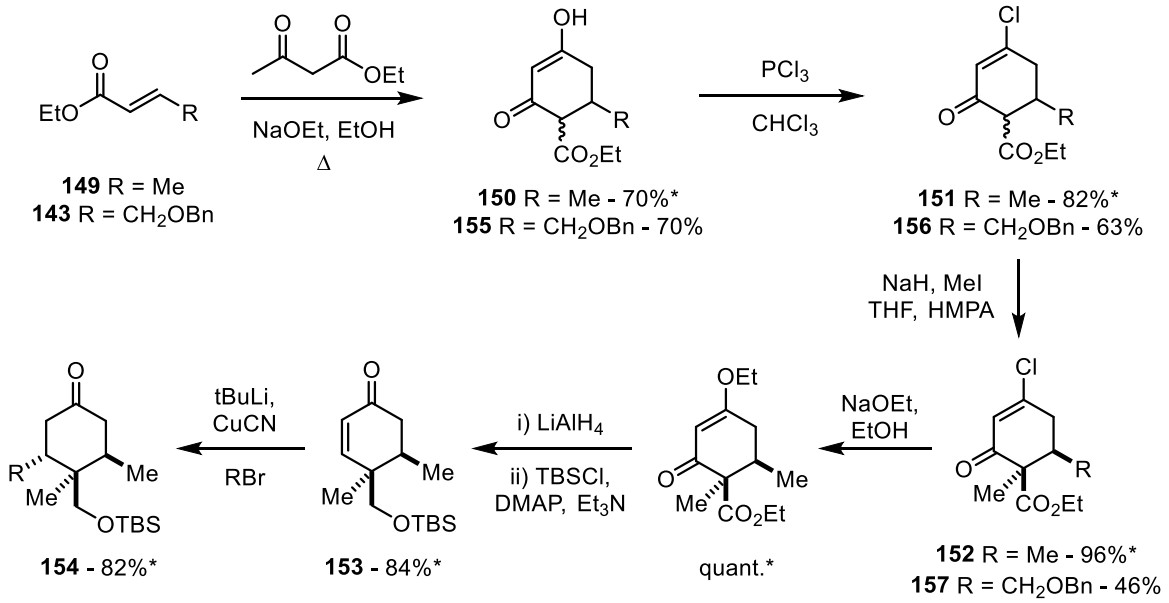


Scheme 77 – Synthesis of unsaturated ester **143** and attempted cyclisation

For the initial cyclisation reaction, ester **143** was prepared via reaction of ethyl but-2-ynoate with benzyl alcohol, triphenyl phosphine and acetic acid (Scheme 77). This reaction has been reported by Trost *et al.* and was developed as a method for the intramolecular formation of

tetrahydrofurans, however can also be applied to intermolecular reactions to give products such as **143**.[175] The mechanism involves a phosphine-catalysed internal redox process. As an initial model reaction, commercially available 4-bromobut-1-ene was used in place of substituted alkylating agent **141**. Unfortunately, reaction of ethyl acetoacetate with 4-bromobut-1-ene followed by **143** resulted only in a complex mixture of products with no clear formation of the cyclised product **148** observed (Scheme 77).

As an alternative, the possibility of alkylating after cyclisation was investigated. A similar strategy featuring in the synthesis of (±)-dysidiolide by Demeke and Forsyth showed that the first two steps can be achieved using a crotyl ester **149** in place of **143** to give **150**.[176] They also report that **150** can then be protected as the vinyl chloride **151** and alkylated at the α-position to give **152**, followed by transposition to the enone **153** which can then undergo conjugate addition to give **154**.

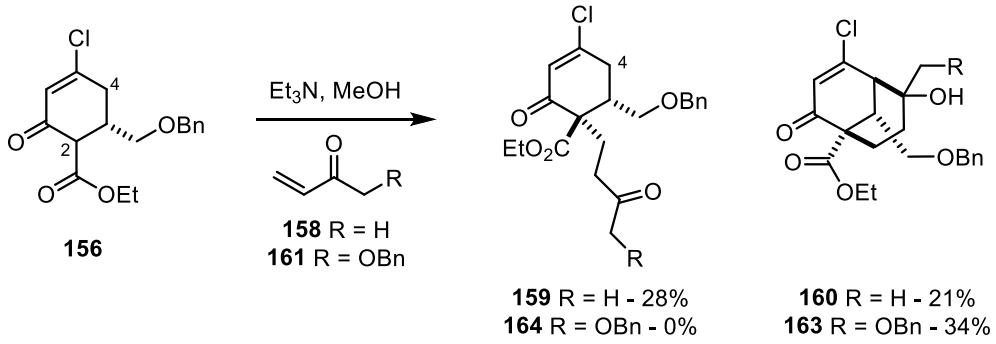


Scheme 78 – Cyclisation and vinyl chloride formation to synthesise **157** following a literature procedure (*literature yield[176])

Cyclisation of **143** with ethyl acetoacetate gave ester **155** in 70% yield which was subsequently converted to the vinyl chloride **156** (Scheme 78). The next step required alkylation of **156** at the α-position. Initial attempts at alkylations using commercially available alkylating agents such as 4-bromobut-1-ene were unsuccessful, and reaction with mesylates gave similar results. Alkylation of similar systems have been reported in the literature with methyl iodide. Reaction of **156** with methyl iodide in the presence of DMPU gave a 46% yield of the methylated product **157** however a higher yielding alkylating method was required.

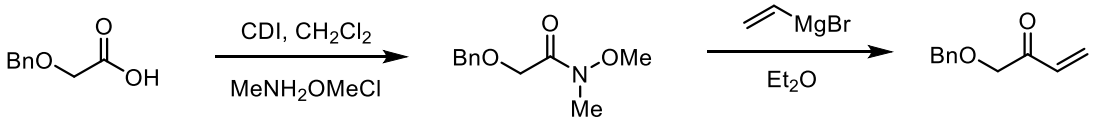
One potential solution was to instead employ a Michael addition with a vinyl ketone **158** to give ketone **159**, a proposed methylenation of the ketone would then give the desired alkene

tether. Initially this reaction was attempted with methylvinylketone **158** to give ketone **159** in 28% yield. Interestingly, as well as the desired product **159**, the cyclised product **160** was also isolated. It was proposed that following the desired Michael addition, deprotonation at C-4 and attack on the side-chain carbonyl would give **160**. **160** was found to have the alternative relative stereochemistry to **159**, implying that both C-2 diastereomers form during Michael addition, and one of these can react further to give alcohol **160**. Despite poor stereocontrol in the Michael addition, formation of alcohol **160** enabled easy separation of the two products.



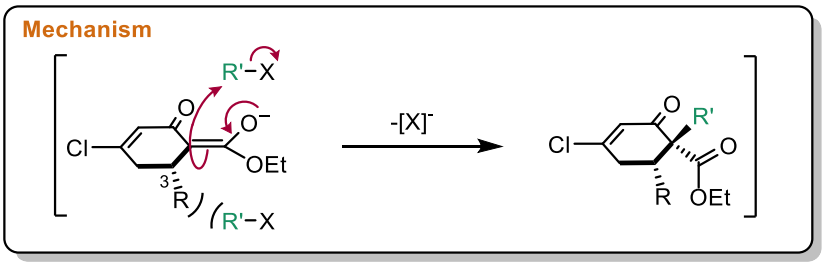
Scheme 79- Michael addition of **156** to **158** or **161**

Benzoxyvinyl ketone **161** was synthesised in two steps through Weinreb amide **162** following a literature procedure (Scheme 80).[177] Reaction of vinyl chloride **156** with **161** in the presence of triethylamine (Scheme 79) unfortunately gave only the cyclised product **163** with no formation of the desired product **164**.



Scheme 80 – Synthesis of **161** via Weinreb amide **162**

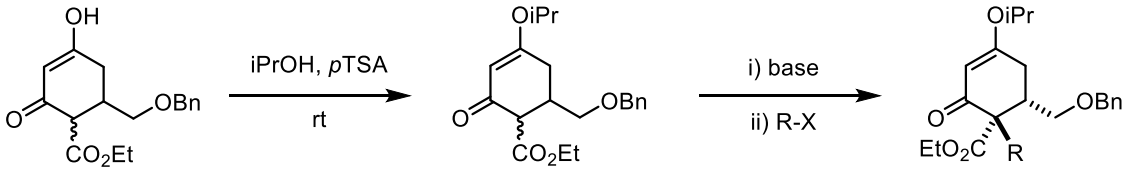
This implies that alkylation of **156** from the top face is preferred, and that use of a bulkier electrophile exacerbates this effect. As can be more easily seen from Scheme 81, alkylation is most likely to proceed from the opposite face to the R-group at the 3-position in order to minimise steric repulsion. This effect was not observed in the alkylation with **158** and seemingly both diastereomers were formed in equal quantities. With a larger R'-group this effect affords complete selectivity for the diastereomer which in this case undergoes a further cyclisation to give **163**. Due to formation of this undesired side product and the low yields obtained, Michael addition as an alkylation method was ruled out.



Scheme 81 – Explanation for the observed selectivity in the alkylation of **156**

Next, the possibility of protecting enol **155** with an alternative group was investigated. Reaction of enol **155** was reacted with *iso*-propanol in the presence of catalytic *p*TSA gave enol ether **165** (Table 9). Use of ethanol was found to give a 3:1 mixture of regioisomers, whilst *iso*-propanol gave a single product.

Table 9 - Protection of **155** as enol ether **165** and alkylation attempts



155

165 - 61%

166 R = allyl
167 R = but-3-enyl

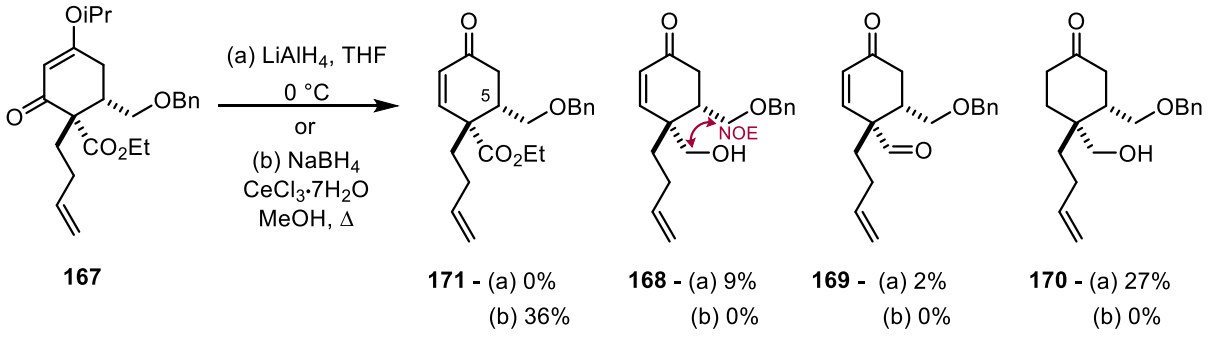
base	R-X	solvent	additive	temp / °C	result
NaH (1.5 equiv.)	allyl bromide (1.5 equiv.)	THF	-	rt	72% (d.r. >20:1)
NaH (10 equiv.)	bromobutene (10 equiv.)	THF	-	66	14% (d.r. 5:1)
NaH (1.5 equiv.)	bromobutene (1.5 equiv.)	DMF	-	rt	NR
NaH (1.5 equiv.)	bromobutene (1.5 equiv.)	THF	NaI (1.5 equiv.)	rt	NR
NaH (1.5 equiv.)	bromobutene (1.5 equiv.)	THF	TBAI (1.5 equiv.)	rt	NR
K_2CO_3 (2.0 equiv.)	bromobutene (1.5 equiv.)	DMF	NaI (1.5 equiv.)	rt	NR
NaOEt (1.5 equiv.)	bromobutene (1.5 equiv.)	EtOH	-	78	NR
NaH (1.5 equiv.)	bromobutene (1.5 equiv.)	DMF	-	153	48% (d.r. >20:1)

Alkylation of **165** was first attempted with allylbromide to confirm that alkylation could proceed successfully, and this indeed showed that the alkylated product **166** was formed in 72% yield with a high level of stereocontrol. This reaction was then repeated with 4-bromobut-1-ene, however it was found that 10 equivalents of both base and alkylating agent along with higher temperatures were necessary before any reaction was observed. Even with these forcing reaction conditions, only 14% of the desired product **167** was isolated with an accompanying decrease in diastereoselectivity. A range of other conditions were investigated, including different solvents, bases, and additives, however in most cases no reaction was observed. Sodium hydride

and 4-bromobut-1-ene in DMF at reflux eventually gave a 48% yield of ester **167** as the only observed product and these conditions were used in further syntheses. The relative stereochemistry of the alkylation product **167** could not be confirmed by ^{1}H-NMR spectroscopy but was assumed to match the selectivity previously observed in similar reactions (Scheme 81). Reaction from the opposite face to the benzyl ether group would result in the stereochemistry of **167** depicted in Table 9.

Although the conditions were successful with 4-bromo-but-1-ene, the target substrate requires additional functionality in the form of an ester or protected alcohol that could be later oxidised. Synthesis of such an alkylating agent, **141**, proved challenging and it was decided to investigate this concurrently with continuation of the synthetic route with **167**. This would allow the next steps to be investigated with the goal of testing the viability of the key photochemical step and, if successful, could also lead to an interesting decarboxy-viburspiran analogue. Synthesis of a suitable alkylating agent **141** is described in further detail in Section 3.3.5.

With **167** in hand, the next step of the synthesis was reduction of the enol ether to give enone **168**. First, lithium aluminium hydride was used but led to a complex mixture of products including the expected product **168**, aldehyde **169** and over-reduced product **170** (Scheme 82). Reduction in the number of equivalents of hydride used was found to have little effect on the selectivity of the reaction. NOE NMR analysis of the enone **168** confirmed that the relative stereochemistry matched the prediction. Although this relative stereochemistry is not that needed for the natural product, it was hoped that upon final oxidation, the stereocentre at C-5 may be epimerised before ring closure, giving the required stereochemistry. Methods to correct this relative stereochemistry were explored later and are discussed in Section 3.3.6.1.



167

171 - (a) 0% (b) 36%

168 - (a) 9% (b) 0%

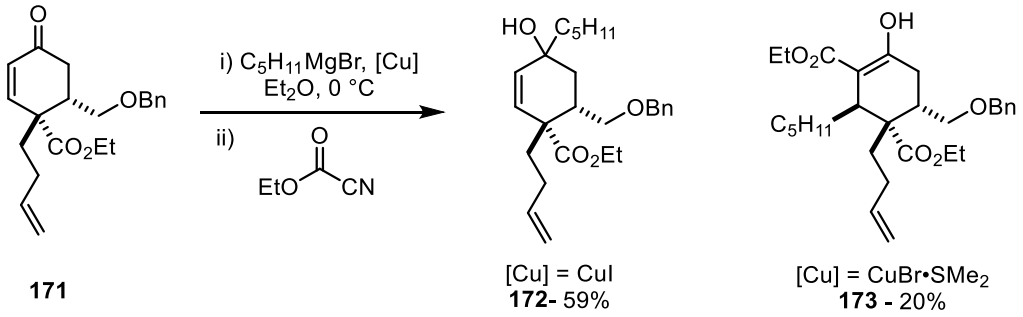
169 - (a) 2% (b) 0%

170 - (a) 27% (b) 0%

Scheme 82 – Enone transposition to form a mixture of reduction products **168-171**

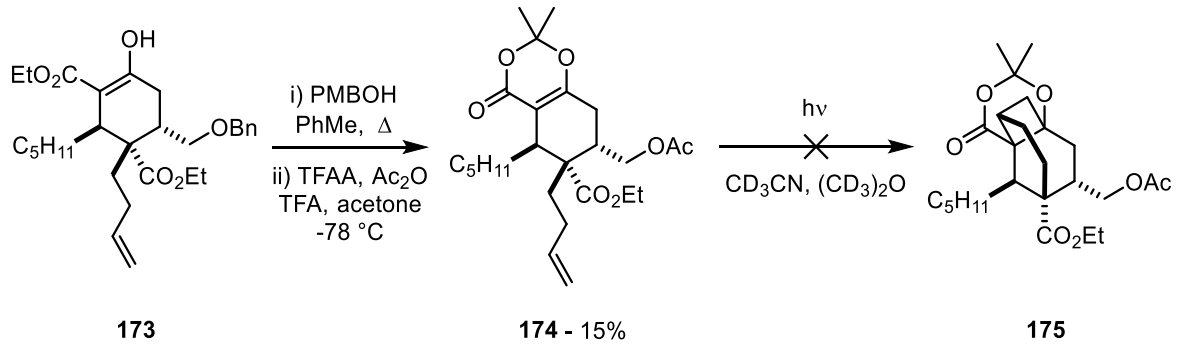
Closer inspection of the literature revealed that sodium borohydride has also been successful in analogous transposition reactions.[178–181] Some involve the use of cerium chloride in a reaction similar to the Luche reduction. These conditions were used for the reduction of **167** to **171**

(Scheme 82), and although the yield for this reaction was low (36%), unlike the previous example using $LiAlH_4$, selectivity was much improved, and no reduction of the ester was observed. The only by-product observed when using cerium chloride was a small amount of decarboxylated product which could be easily removed, and its formation was suppressed at lower temperature.



Scheme 83 – Conjugate addition reaction to install pentyl chain and ester **173**

Conjugate addition to enone **171** with pentylmagnesium bromide and a copper halide, followed by addition of a cyanoformate to introduce the α-ester was then carried out (Scheme 83). Copper iodide gave only formation of the 1,2-addition product **172**, however CuBr•SMe_2 gave the desired product **173** in 20% yield but good diastereoselectivity. From the ^{1}H-NMR and NOE-NMR data, it was unclear which diastereomer of **173** had been isolated from the conjugate addition reaction. Ley *et al.* had previously shown that conjugate addition of similar 4,4,5-trisubstituted cyclohexenones with the same relative stereochemistry undergo attack from the top-face to give the diastereomer shown in Scheme 83.[182] The same selectivity has been reported for conjugate additions with esters at the 4-position in numerous total syntheses and so the relative stereochemistry of **173** has been inferred from the literature.[183–185]

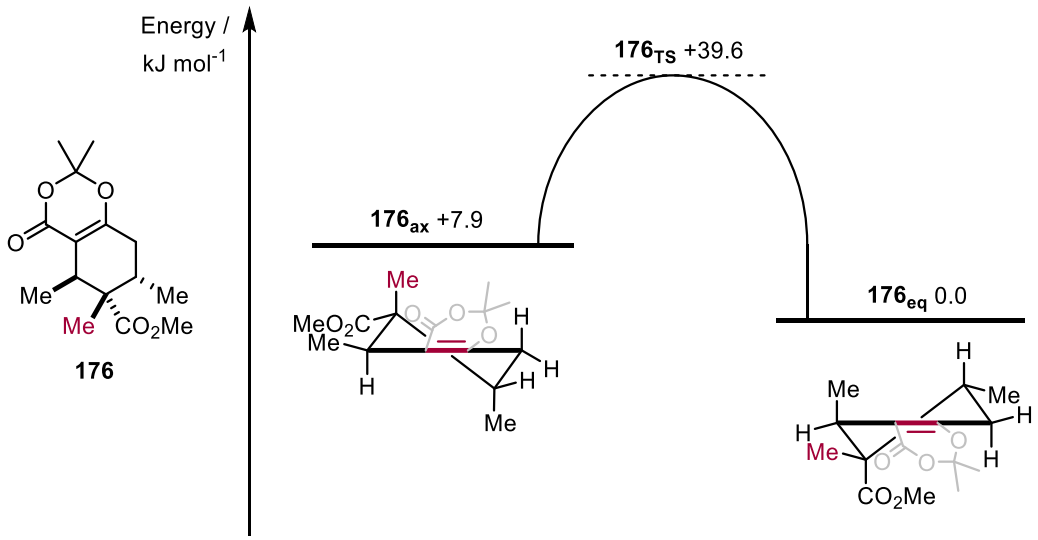


Scheme 84 – Formation of dioxenone **174** and photochemical cyclisation attempt

Dioxenone formation was carried out in a similar manner to that used for the model substrates, involving transesterification to the PMB ester, followed by reaction with acetone under acidic conditions (Scheme 84). Dioxenone **174** was isolated in 15% yield over the two steps. The low yields were as mainly attributed to a large amount of PMB-side product as had

been observed when this reaction was previously carried out. Interestingly, the benzyl group was removed during the reaction and had been replaced by an acetate. The small amount of **174** successfully synthesised was subjected to photochemical conditions however unfortunately, upon irradiation, no conversion to **175** was observed.

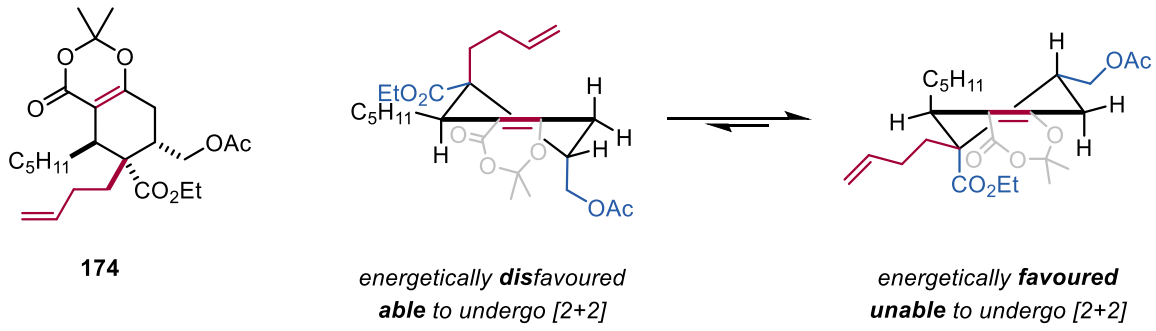
To investigate this unexpected result, DFT calculations (Gaussian 09, DFT: B3LYP,6-31G)[186] were carried out to determine the conformation of the dioxenone **174**. A simplified version of the dioxenone **176** was used in order to minimise the degrees of rotational freedom and therefore make the calculations less computationally time-consuming. Both ring flip conformations $\mathbf{176_{ax}}$ and $\mathbf{176_{eq}}$ were considered and named based on the position of the 4-methyl group which corresponds to the reactive alkene in the photochemical reaction of **174**. It was hypothesised that the orientation of this alkene group is crucial in the success of [2+2]-cyclisation with the dioxenone.



Scheme 85 – Energies for ring-flip conformations $\mathbf{176_{ax}}$ and $\mathbf{176_{eq}}$ and the TS energy (DFT: B3LYP,6-31G)

Energy minimisation of $\mathbf{176_{ax}}$ and $\mathbf{176_{eq}}$ showed that $\mathbf{176_{eq}}$ was around 7.9 kJ mol^{-1} lower in energy than $\mathbf{176_{ax}}$, which could be as a result of the slightly smaller ester group preferentially occupying an axial conformation. A transition state for the ring-flip was located and found to be around 40 kJ mol^{-1} higher in energy than the $\mathbf{176_{eq}}$ conformation (Scheme 85). Therefore, the equilibrium between the two conformers will be in favour of the more stable conformer $\mathbf{176_{eq}}$. Extrapolating these results to the synthesised substrate **174** could explain why the photochemical reaction was unsuccessful. If the same conformation is thermodynamically dominant for **174** as was calculated for **176**, this would mean the alkenyl chain is predominantly in an equatorial position. In this conformation the alkene is unable to come within bond-forming distance of the dioxenone in the way required for successful [2+2]-cyclisation. Conversely, the axial conformer would allow the alkene to come into close proximity with the dioxenone,

however it may not be thermally accessible in this system. There are some limitations to this argument; the calculations were carried out with a simplified model substrate which may affect results. It would be assumed however that bulkier substituents around the ring would have the effect of increasing the TS energy for ring flip and therefore make this effect even more profound. Another limiting factor is the effect of photochemical excitation on the substrate. In the [2+2]-photocyclisation, the biradical that forms could display a different conformational preference and so computational studies could be repeated on the biradical intermediate rather than **176** to give more accurate results.



174

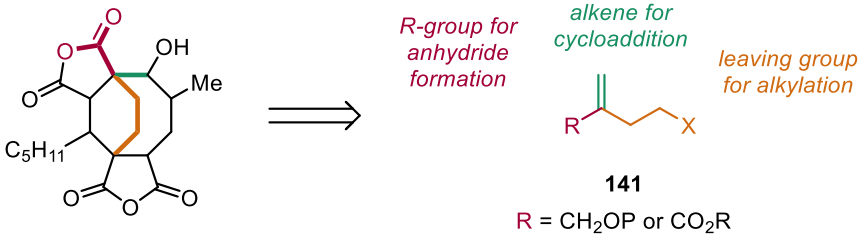
*energetically **dis**favoured*
***able** to undergo [2+2]*

*energetically **favoured***
***unable** to undergo [2+2]*

Scheme 86 – Possible conformers of dioxenone **174** and their ability to undergo [2+2]-cyclisation

3.3.5. Synthesis of a Suitable Alkylating Agent

Previous alkylations in this route have used commercially available alkylating agents such as 4-bromobut-1-ene, which allows incorporation of the ethylene bridge into the carbocyclic structure of viburspiran by [2+2]-photocycloaddition. Ideally the alkylating agent would also include an R-group suitable for transformation to an anhydride later in the synthesis (Scheme 87). Along with this, the alkylating agent needs a suitable leaving group, along with the alkene required for cycloaddition.



72

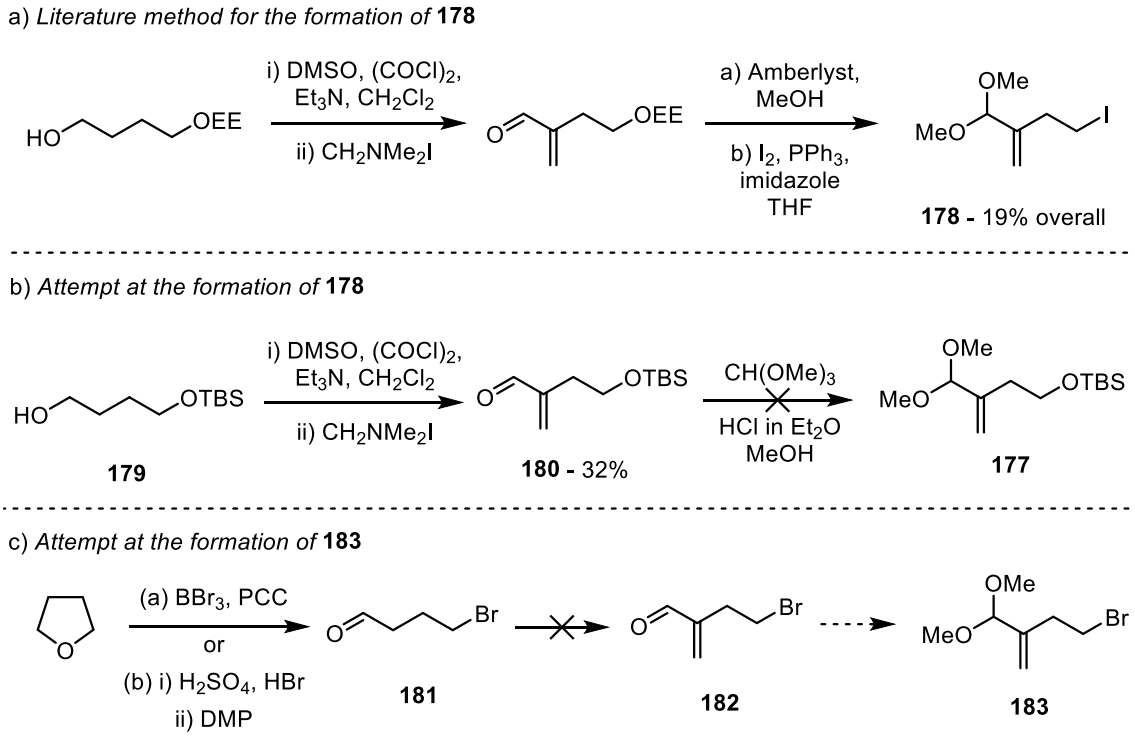
141
R = CH_2OP or CO_2R
X = Br, I, OTs, OMs

Scheme 87 – Structural requirements for a fully functionalised alkylating agent with the general structure **141**

Despite the simple structure, methods to synthesise such molecules are rare in the literature and synthesis of a suitable alkylating agent was more challenging than originally anticipated. The first attempt was of the synthesis of silyl ether **177** which incorporates the R-group as a dimethyl acetal protected aldehyde. Synthesis of iodide **178** has been previously reported and

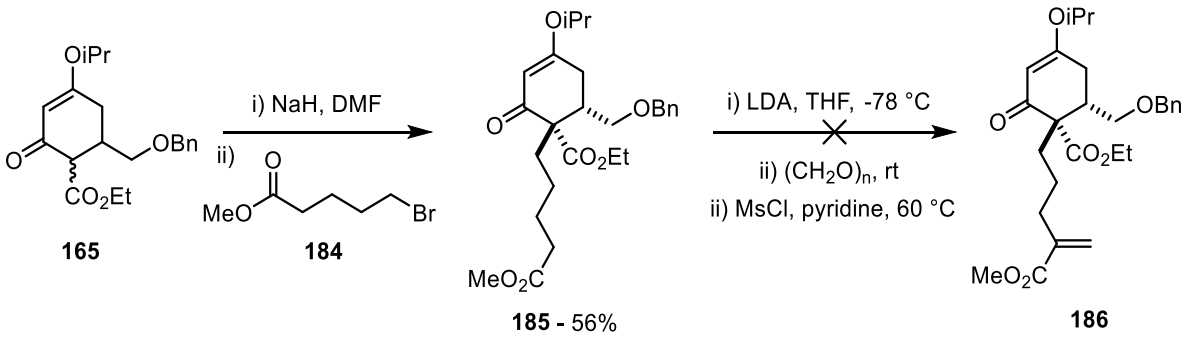
uses an oxidation-methylenation strategy to incorporate the corresponding functional groups (Scheme 88a).[187]

Use of this methodology was hampered by the availability of reagents necessary to synthesise the ethoxyethyl acetal (EE) protecting group. The same methodology was instead carried out with the TBS-protected diol **179**. Oxidation and subsequent methylenation gave aldehyde **180** in 32% yield. Attempted protection of the aldehyde as the dimethyl acetal failed and led only to deprotection of the TBS-ether and some evidence of cyclisation products (Scheme 88b). Using an alternative approach, it was shown that THF could be ring opened under acidic conditions, either to give aldehyde **181** directly,[188] or through formation of the alcohol followed by oxidation to **181**.[189] Methylenation of **181** to give **182** was unsuccessful and only resulted in degradation of the starting material (Scheme 88c).



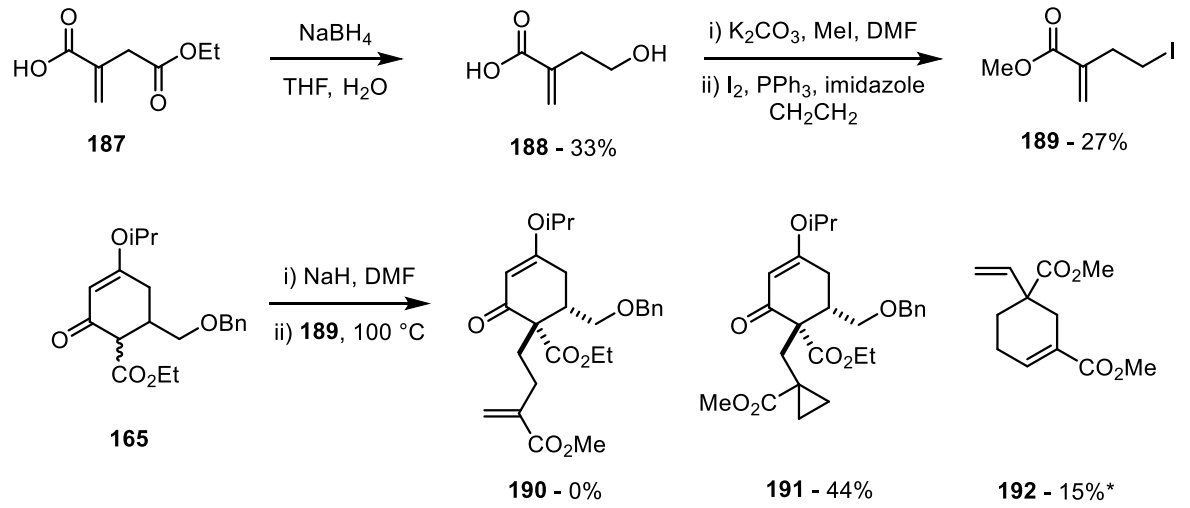
Scheme 88 – Synthesis of dimethyl acetal alkylating agent **178** or **183**

Due to the issues with α-methylenation of aldehydes prior to alkylation, it was proposed that methylenation could be carried out after alkylation. Hence, ester **165** was alkylated with commercially available bromide **184** (methyl 5-bromopentanoate was used for this test in place of methyl 4-bromobutanoate due to availability)(Scheme 89). Alkylation under these conditions proceeded smoothly and gave diester **185** in 56% yield. Methylenation of **185** resulted only in degradation of the starting material and no formation of desired product **186**.



Scheme 89 – Alkylation followed by α-methylenation of the terminal ester of **185**

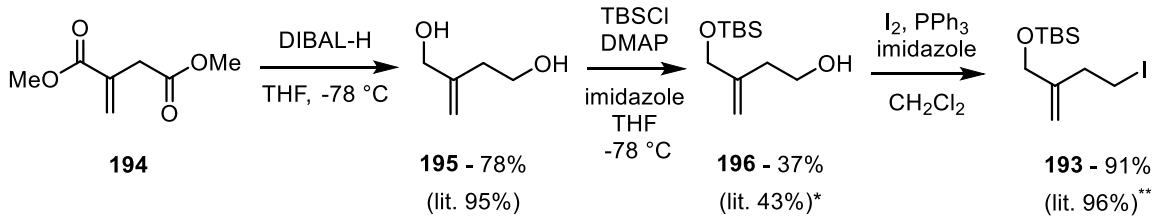
A final strategy investigated for the synthesis of a suitable alkylating agent was to start from commercially available itaconic acid and its ester derivatives. Initially, monoethyl itaconate **187** was reduced using sodium borohydride to give **188**, followed by methylation of the carboxylic acid and an Appel reaction to form iodide **189** (Scheme 90). Alkylation of **165**, under the same conditions that have been previously successful were used, gave no formation of the desired alkylated product **190**. Instead, a considerable amount of the cyclopropane product **191** was isolated, which results from Michael addition followed by cyclisation of the resulting enolate onto the alkyl iodide.[190] **192** was also isolated as a result of elimination and Diels-Alder reaction of **189**.



Scheme 90 – Synthesis of ester alkylating agent **189** and unsuccessful alkylation (*yield w.r.t. **189**)

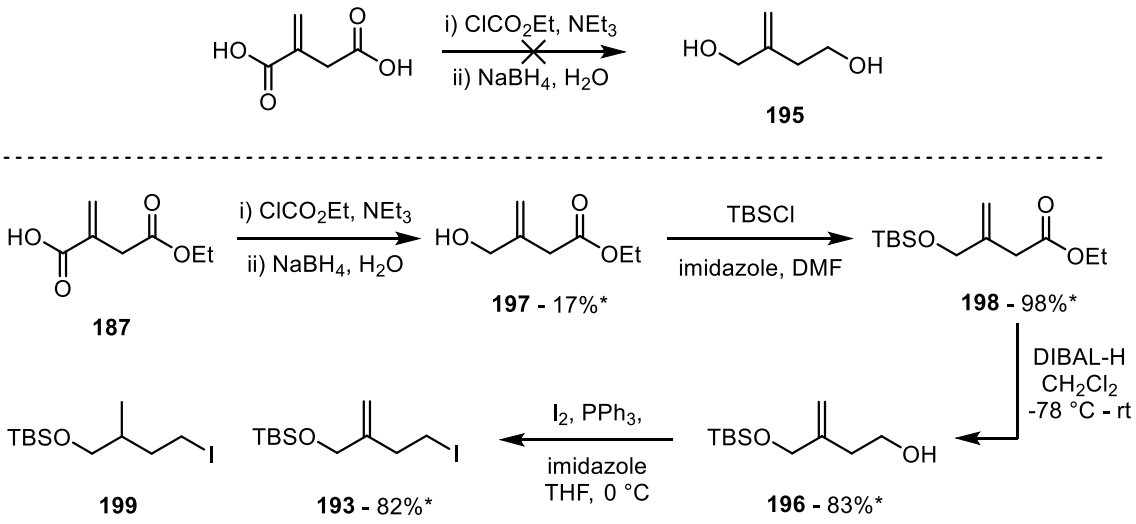
Based on this result, both unsaturated esters and protected unsaturated aldehydes had now been ruled out as options for an easily accessible electrophile. One of the final options was to use a protected alcohol, which would require oxidation at a later stage in the synthesis. This was not deemed unreasonable, as other functionality would need the same modification at a late stage in order to form the anhydride units. A literature method for the synthesis of iodide **193** has been reported (Scheme 91).[191,192] This approach was carried out on a small scale and similar results to the literature were achieved. DIBAL-H reduction of dimethyl itaconate **194**

gave diol **195** in 78% yield. TBS protection to give **196** was carried out with conditions that had previously been shown to be selective for allylic alcohols, however no major improvement in yield was observed (37% vs 43%).[193] By-products from this reaction, namely the di-protected alcohol and the undesired regioisomer can be recycled by conversion back to the diol using TBAF. Appel reaction of **196** with iodine and PPh_3 gave iodide **193** in 91% yield. Alkylation and continuation of the route with **193** is discussed in Section 3.3.6. Although this route was successful in forming a suitable alkylating agent, concerns with the scale up of the DIBAL-H reduction meant that alternative methods of reduction were investigated.



Scheme 91 – Synthesis of iodide **193** from dimethyl itaconate
(*TBSCl, NaH, THF, 10 °C **I_2, PPh_3, imidazole, CH_3CN/Et_2O 3:1)

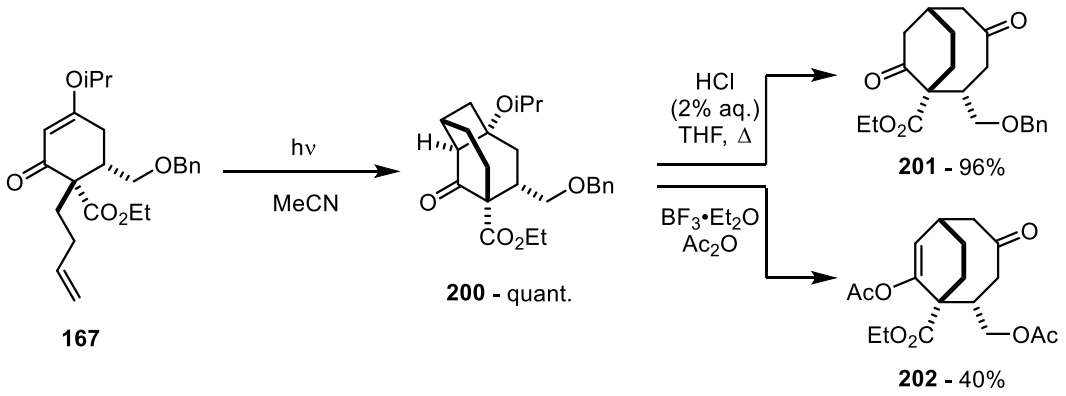
One method involves reduction of a mixed anhydride of itaconic acid, by reaction with ethyl chloroformate followed by addition of sodium borohydride. This reaction gave none of the required diol **195**, so instead the reaction was repeated with monoethyl itaconate **187** (Scheme 92). This reaction was low-yielding (17%) and the product was isolated as a 1:0.6 mixture of **197** and the inseparable 1,4-reduction product. Despite this, the starting material is inexpensive (£1.75/g Fluorochem), and the reaction can be carried out safely on a large scale which makes it appealing as the initial step in the total synthesis. For these reasons, the mixture was carried through and pleasingly the subsequent protection (to give **198**), reduction (to give **196**) and Appel reactions all proceeded in excellent yields to give **193** which was also isolated as a 1:06 ratio of **193** to the saturated iodide **199**. This by-product was found to be inseparable through all stages of this route and was present in the same ratio throughout. Theoretically **199** could be carried through the synthesis until the photochemical step where the resulting product would not undergo [2+2]-cyclisation and at this point, it was hoped, the products would become separable. Subsequent steps carried out on this mixture of **193** and **199** are detailed in Section 3.3.6.



Scheme 92 – Mixed anhydride method for the synthesis of **193** and formation of saturated by-product **199** (*Present as a 1:06 ratio of unsaturated to saturated products)

3.3.6. Second Generation Synthetic Route

As the key photochemical step with dioxenone **174** failed, the synthetic route was revisited in order to establish alternative options. It was realised that previously synthesised intermediate **167** on the pathway, may in fact be able to act as a chromophore in [2+2]-cycloadditions in a similar manner to the dioxenone. Enol ethers have been used successfully in similar intramolecular cycloaddition and de Mayo ring openings, for example in the synthesis of (±)-longifolene and (±)-daucene (Scheme 59).[142,143]

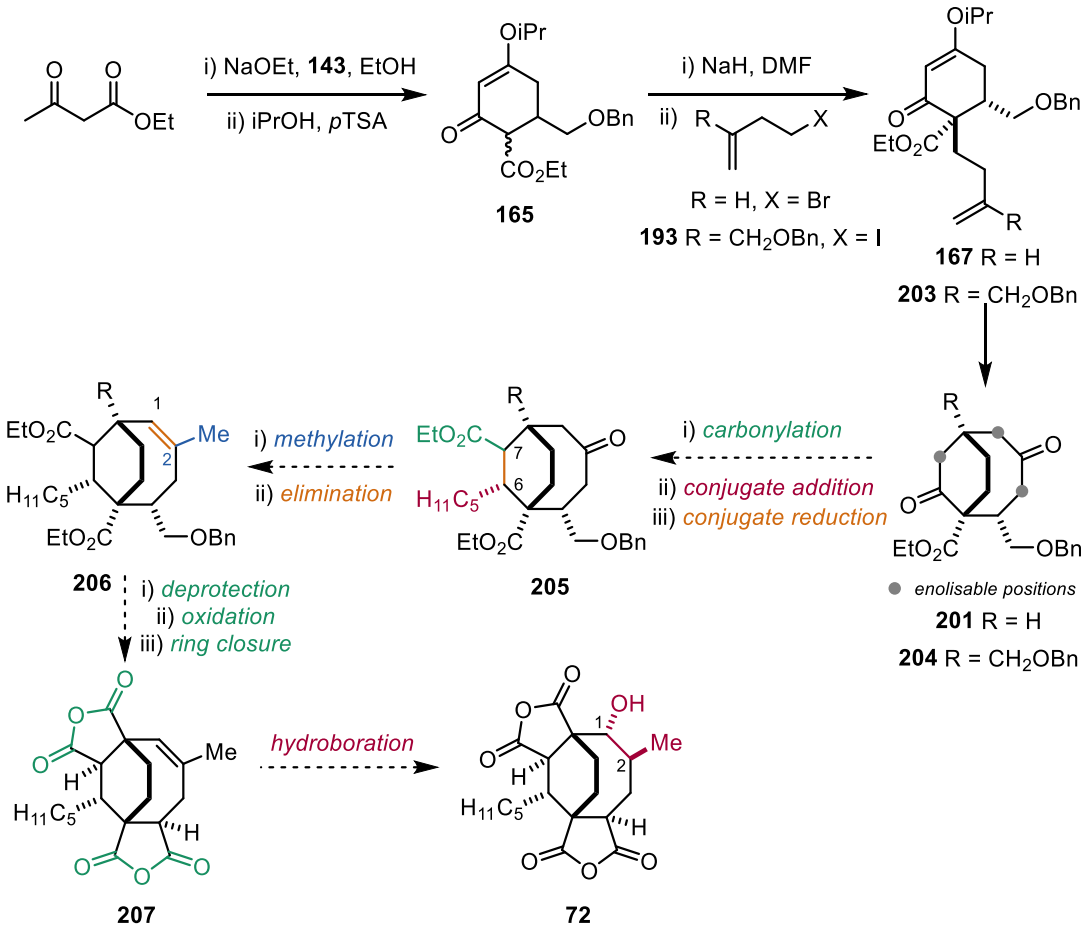


Scheme 93 – Photochemical irradiation of **167** to form **200** and retro-aldol reaction to give **201** or **202**

Irradiation of **167** under UV-light gave complete conversion to cyclobutane **200** (Scheme 93). It was also found that acetone was not necessary as a sensitiser for this reaction and the transformation could be carried out in acetonitrile. Treatment of **200** with 2% HCl (aq.) gave the ring opened product **201** in 96% yield. The cyclobutane **200** could also be ring opened in the presence of acetic anhydride to give **202** in a 40% yield. Synthesis of **201** provided confirmation that the proposed key step in the total synthesis was feasible and allowed synthesis of the core structure of viburspiran with functionality in place to install most of the remaining moieties.

The remainder of the proposed synthetic route to viburspiran was revisited and modified to take the success of this reaction into account (Scheme 94). Alkylation with the now synthesised alkylating agent **193** would give **203** which was expected to undergo photochemical [2+2]-cycloaddition and ring opening to give **204**. From there, several modifications are necessary on both sides of the molecule. The presence of two ketones and three acidic positions was acknowledged and it was hoped the three-dimensionality of the molecule and other proximal substituents may help to bias reactivity. The order in which the subsequent modification steps could be carried out was flexible and so several options were explored.

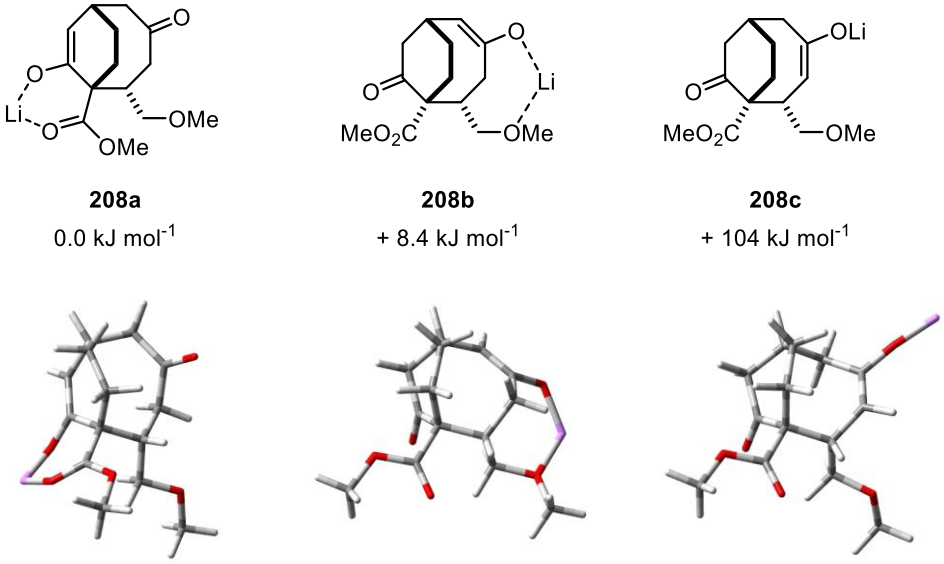
On the left-hand-side (as drawn, Scheme 94), deprotonation at the α-position (C-7) and reaction with a chloro- or cyanoformate would allow incorporation of the remaining ester. Following this, formation of the enol triflate would then allow introduction of the pentyl chain at C-6 through a conjugate addition, and subsequent conjugate reduction of the alkene would give **205**. Based on three-dimensional models of the precursor to **205**, the top face appears less sterically hindered and so conjugate reduction is predicted to occur to give the desired diastereomer.



Scheme 94 – Revised plan for the synthesis of viburspiran based on photochemical cyclisation of **167**

On the right-hand-side, addition of either methyllithium or methylmagnesium bromide would form the tertiary alcohol, which could then be eliminated to give the endocyclic olefin **206**, followed by a series of transformations to the anhydride rings in **207**. A mixture of regioisomers of **206** could form during the elimination step, however if successful, this should allow for a simple hydroboration-oxidation to incorporate the alcohol at C-1 as the final step in the synthesis.

To preserve synthetically valuable alkylating agent **193**, several of the modification steps were first investigated on the slightly simpler diketone **201**, which could be readily synthesised using commercially available 4-bromobut-1-ene. The first of these was the introduction of an ester at C-7, which required deprotonation at this position. Due to the presence of a second ketone at C-2 with two possible acidic positions, any selectivity was unclear. To investigate the effects of thermodynamics on selectivity, DFT studies (Gaussian 09, DFT: B3LYP,6-31G)[186] on the possible enolates that could result from deprotonation was carried out.

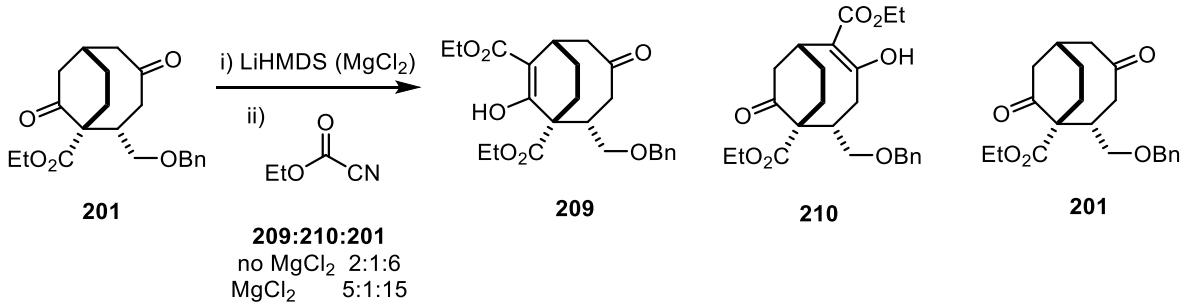


Scheme 95 – Relative energies of geometry optimised (DFT: B3LYP,6-31G) lithium enolates **208a-c** and their stabilising interactions

Optimisation of the structures of enolates **208a-c** and comparison of the minimised energies made it clear that thermodynamically, **208a** is the most stable enolate due to the stabilisation afforded by the ester (Scheme 95). **208b** is 8.4 kJ mol^{-1} higher in energy than **208a** with some stabilisation provided by an interaction with the ether lone pair. Lithium enolate **208c** cannot be stabilised by either the ether or ester and is therefore significantly higher in energy.

Based on the computational evidence, it was considered worth attempting a selective deprotonation of diketone **201** (Scheme 96). Addition of LiHMDS followed by ethyl cyanoformate resulted in formation of the desired product **209**, along with some of the

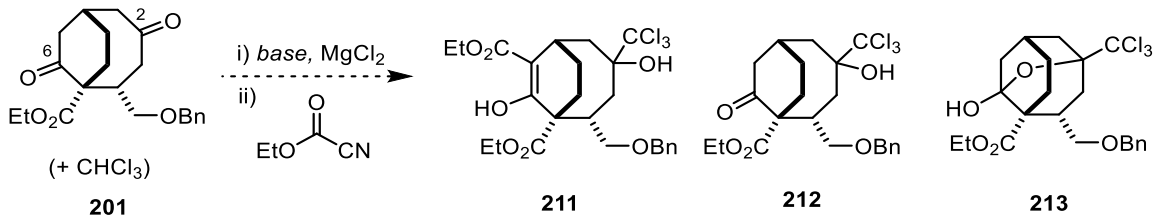
regioisomer **210**, which was inseparable from **209**, and unreacted starting material **201** in a 2:1:6 ratio (**209:210:201**). In an attempt to increase the regioselectivity of the reaction, magnesium chloride was added to coordinate to both the enolate, and the neighbouring ester carbonyl and therefore stabilise the desired enolate. Pleasingly this led to increased selectivity from 2:1 to 5:1 for the two regioisomers (Entries 1 & 2, Scheme 96). The reaction time was also increased from 3 to 16 h, however this was found to have little effect on the conversion and an appreciable amount of starting material was recovered in each case.



Scheme 96 – Regioselectivity in the carbonylation of **201** using a coordinating additive

Regioisomers **209** and **210** were inseparable by column chromatography, so conditions that afforded even higher selectivity were needed. Alternative bases such as LDA, NaHMDS and KHMDS were also tested in case the size of the counterion influenced enolate stability. Unfortunately, in these reactions an alternative batch of starting material was used that was found to contain residual chloroform, presumably from NMR analysis. Despite preventing formation of the desired product, the residual chloroform caused formation of some interesting side-products that gave valuable insight into the reactivity of **201**.

With LDA, no desired product was observed but formation of **211** and **212** occurred, and with NaHMDS and KHMDS, **213** was also isolated (Scheme 97). Interestingly, products **211**, **212** and **213** all contain a CCl_3 group, the presence of which was confirmed by HRMS. Under basic conditions, chloroform can be deprotonated and act as a nucleophile, resulting in addition to the carbonyl as observed in **211**, **212** and **213**.[194–197]

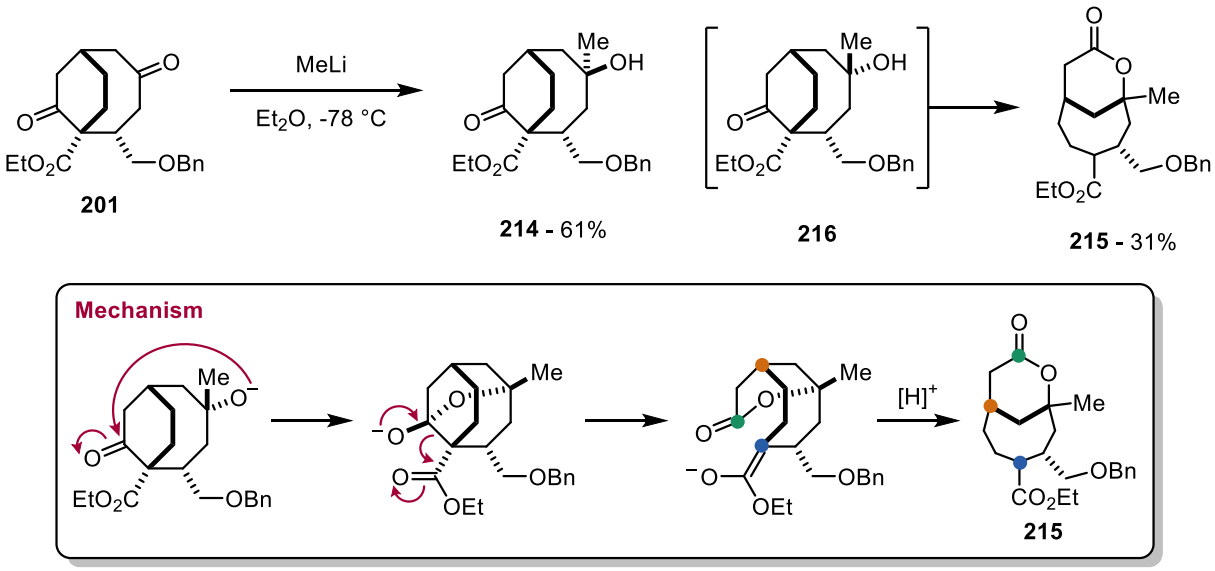


Scheme 97 – Products formed in the attempted carbonylation of **201** with residual chloroform present

In the formation of **211**, the desired carbonylation reaction had also taken place. Isolation of **212** and **213** occurred concurrently with no formation of desired product **209**, so it can be assumed the reaction with chloroform is faster than the carbonylation reaction and that this

occurs first, followed by the carbonylation. **213** is formed by **212** undergoing an intramolecular hemi-acetal formation by reaction of the C-2 alcohol with the C-6 ketone. Transannular reactions in similar eight-membered rings have been previously reported.[198,199] To prevent formation of these chloroform related side products, the starting material was more rigorously dried and the reaction repeated. However, ^{1}H-NMR analysis of the crude material showed a complex mixture of products with no formation of any previously observed products, including no recovery of starting material.

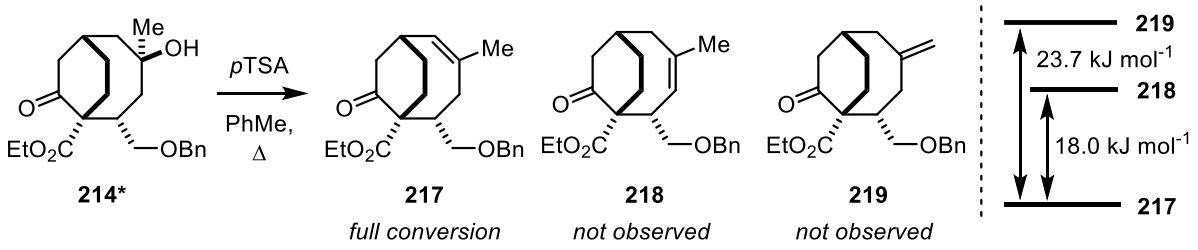
Although the carbonylation of **201** gave mixed results and was somewhat complicated by the presence of residual chloroform in the reaction, these results provided valuable insights into the reactivity of **201**. In the presence of a CCl_3 anion, nucleophilic addition proceeded exclusively at C-2, with no C-6 addition product observed in any of the reactions. This attack also seemed to occur faster than the desired carbonylation reaction, which was never observed to reach completion. Since the transformation necessary at the C-2 position involved methylation, it was proposed that conducting this reaction first may be more successful in both yield and selectivity.



Scheme 98 – Methylation of **201** to form **214** and further reaction of diastereomer **216** to give **215**

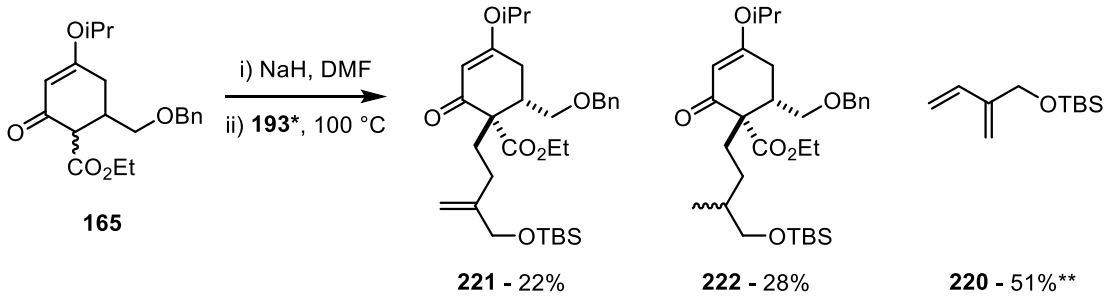
Reaction of **201** with methyllithium resulted in selective addition to the C-2 ketone to give desired product **214** and no evidence of reaction at the C-6 ketone was observed (Scheme 98). As the next step of the sequence is elimination, the stereoselectivity in this reaction was unimportant, however it did demonstrate an interesting result. Isolation of side product **215** indicated that one of the diastereomers formed, **216**, was able to undergo transannular acetal formation, as had been previously observed (Scheme 97). However, in this case, further ring-opening of the hemi-ketal with use of the C-5 ester, allowed **215** to be formed as the

by-product for this reaction. The excellent mass recovery achieved in this reaction indicates that the desired transformation is successful and with 2:1 selectivity for the stable diastereomer **214**.



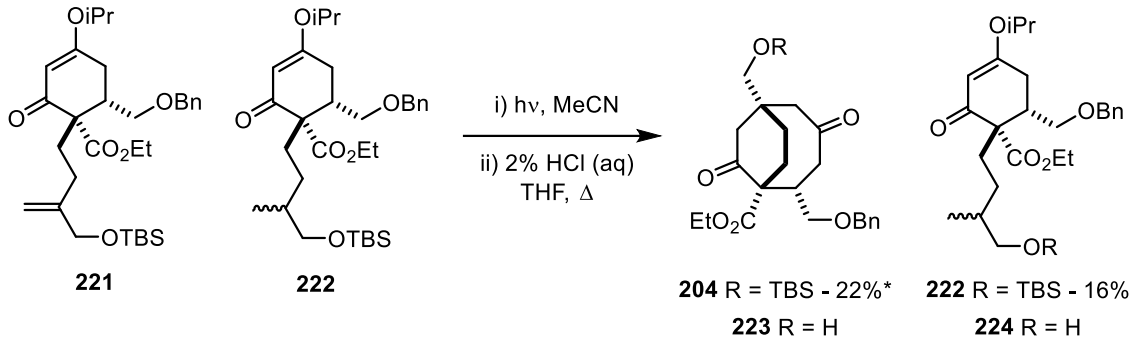
Scheme 99 – Elimination of **213** to give possible products **217**, **218** and **219** and DFT prediction of the result (*10 mg of a 2:1 mixture of **214** and **215** used)

Elimination of the tertiary alcohol could in theory occur to form one of three alkenes. DFT calculations were again used to help predict the regiochemistry of this step before it was carried out. Geometry optimisation (Gaussian 09, DFT: B3LYP,6-31G)[186] of the three possible products **217**, **218** and **219** was carried out and showed that the desired alkene **217** was the lowest in energy and would therefore be the expected thermodynamic product of the reaction, however transition state energies for each of the possible elimination routes were not considered here due to time constraints. Heating **214** with *p*TSA in toluene (**214** and **215** were unfortunately inseparable so this reaction was carried out on a 2:1 mixture respectively on an ^{1}H-NMR sample scale) gave full conversion to 217 and the regioselectivity of the reaction was confirmed by 2D-NMR. Recovery of **215** from this reaction was also observed.



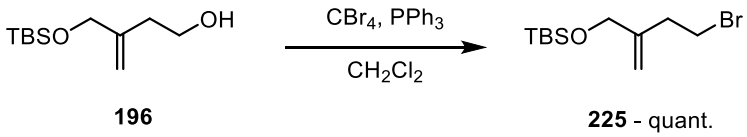
Scheme 100 – Alkylation of **165** with **193** and **199** to give **221** and **222** (*1:0.6 ratio of **193**:**199**, **51% with respect to **193**)

With these promising results for modification of the RHS of the molecule, attention turned to alkylation with the fully functionalised tether **193** (Scheme 100). Initially, the alkylation was carried out with **193** isolated from the mixed anhydride reduction route, which was a 1:0.6 ratio of saturated and unsaturated iodides **193** and **199**. Unfortunately, upon alkylation of **165** elimination of **193** occurred to form diene **220** accounting for 51% of the unsaturated iodide **193** added. This meant that although the alkylation was successful, the ratio of unsaturated to saturated alkylation products **221**:**222** was now 1:1.3 in favour of **222**.



Scheme 101 – Photochemical reaction of a 1:1.3 mixture of **221** and **222** followed by ring-opening (*Yield of **204** relative to amount of **221** in the mixture)

Unfortunately, as **221** and **222** were inseparable by column chromatography and due to the presence of a chiral centre in the saturated side chain of **222**, a complex mixture of **221** and diastereomers of **222** made characterisation difficult and the product mixture was carried immediately through to photochemical cyclisation. Photochemical irradiation of the mixture followed by ring opening under acidic conditions gave 22% of **204** from **221** and 16% recovery of **222** (Scheme 101). The majority of material isolated from this two-step sequence was a mixture of **223** and **224** in which deprotection of the TBS-group had occurred.

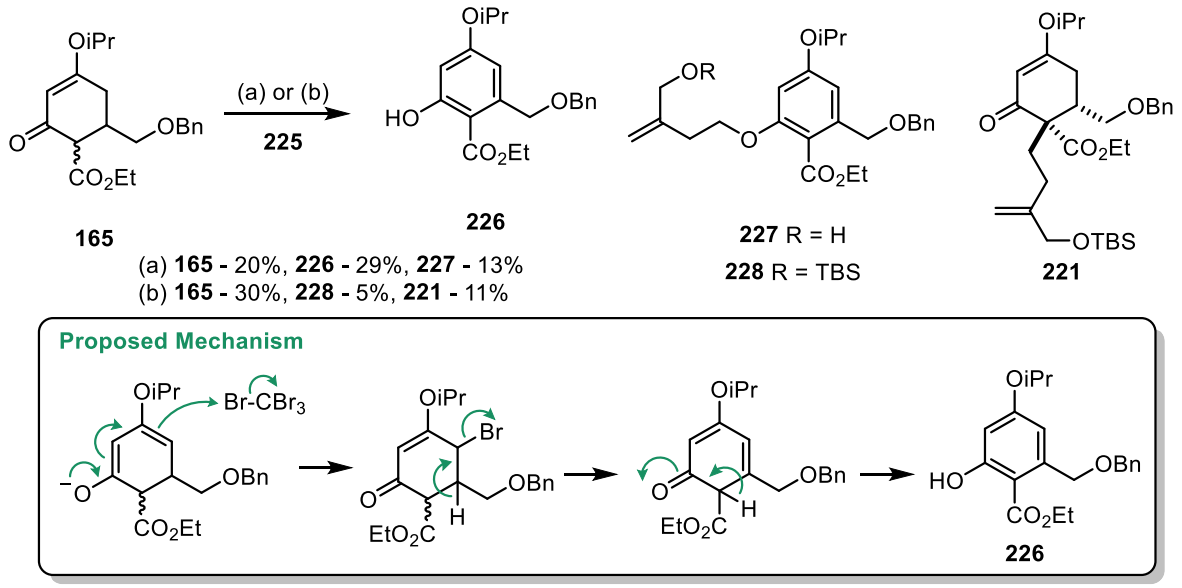


Scheme 102 – Synthesis of bromide alkylating agent **225**

These results showed that the presence of the saturated alkylating agent **199** was not as benign as anticipated, and although the alternative method required a large scale DIBAL-H reduction (Scheme 91), using a pure alkylating agent would lead to fewer issues with inseparable side products. In addition to this, methods to avoid the elimination of alkylating agent **193** were also investigated. One such method was to synthesise the alkyl bromide **225** in a hope that elimination of the bromide would occur less readily than with the iodide.

Optimisation of the alkylation reaction with bromide and iodide **225** and **193** was then carried out. Bromide **225** was investigated first as it was hoped that elimination to the diene **220** may be less likely to occur. Sodium hydride and caesium carbonate were used as bases and in both cases, aromatised products **226**, **227** and **228** were observed, with a small amount (11%) of the desired product **221** formed when Cs_2CO_3 was used (Scheme 103). Aromatisation of **165** was unexpected and had not been observed previously with alkyl iodide **193.** It was hypothesised this may be due to an impurity present in **225**. Presence of an electrophilic source of bromine arising from the Appel reaction to form **225** could allow bromination of **165** which

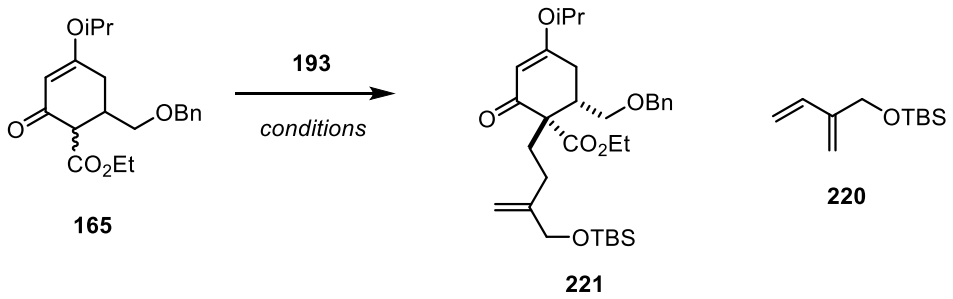
could facilitate aromatisation. Following formation of **226**, alkylation with **225** would form **228**. Under sodium hydride conditions, deprotection of the TBS group was observed to form **227.**



Scheme 103 – Attempted alkylation of **165** with **225** resulting in aromatisation to form **226** and **227** or **228.** (a) – NaH, DMF, 100 °C, (b) – Cs_2CO_3, MeCN, 60 °C

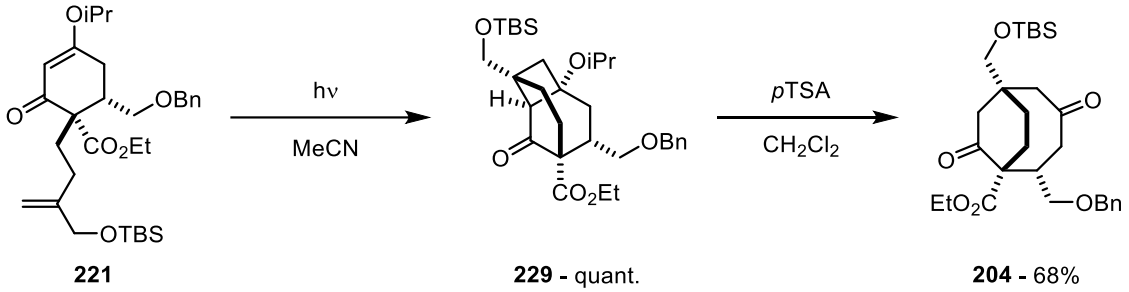
The alkylation was then re-investigated with alkyl iodide **193** synthesised through the method shown in Scheme 91. The reaction was conducted at room temperature to begin with in order to reduce formation of eliminated product **220**. This gave 24% of the desired product **221**, with 12% recovery of starting material and 10% formation of the diene **220** (Table 10). At this point alternative alkylation conditions were trialled, and it was found that the yield could be increased to 44% with Cs_2CO_3 in acetonitrile at 60 °C. Starting material **165** was also recovered, but the overall mass recovery was better than when sodium hydride was used, meaning that the starting material recovered could be recycled. It was also found that this reaction scaled favourably with a 59% yield (91% BRSM) achieved when the reaction was carried out on a 12.5 mmol scale. (For entries 3 & 4, Table 10, **220** was not isolated but found to be present in a similar ratio to entry 2 based on the ^{1}H-NMR of the crude material.)

Table 10 – Alkylations of **165** with **193**



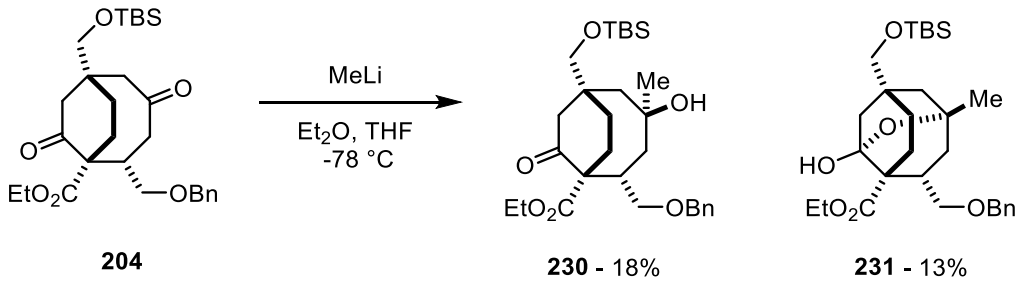
entry	conditions	scale / mmol of 165	165 (%)	221 (%)	220 (%)
1	NaH, DMF, rt, 48 h	0.25	12	24	10
2	Cs_2CO_3, MeCN, 60 °C, 65 h	1.50	27	44	14
3	Cs_2CO_3, MeCN, 60 °C, 65 h	4.50	39	40	-
4	Cs_2CO_3, MeCN, 60 °C, 65 h	12.5	35	59	-

Following successful alkylation, enol ether **221** was subjected to UV-light and successfully reached 100% conversion after 6 h (Scheme 104). Cyclisation product **229** was found to be unstable and sensitive to slightly acidic conditions (e.g. chloroform or silica gel) and so full characterisation of **229** was not pursued and instead it was immediately ring-opened to **204**. With the simpler photochemical product **200**, 2% HCl (aq.) in THF at reflux had been used to achieve the retro-aldol reaction, however the previously observed issues with TBS-deprotection meant that these conditions were no longer feasible. The same transformation could instead be achieved by stirring with *p*TSA in dichloromethane at room temperature.



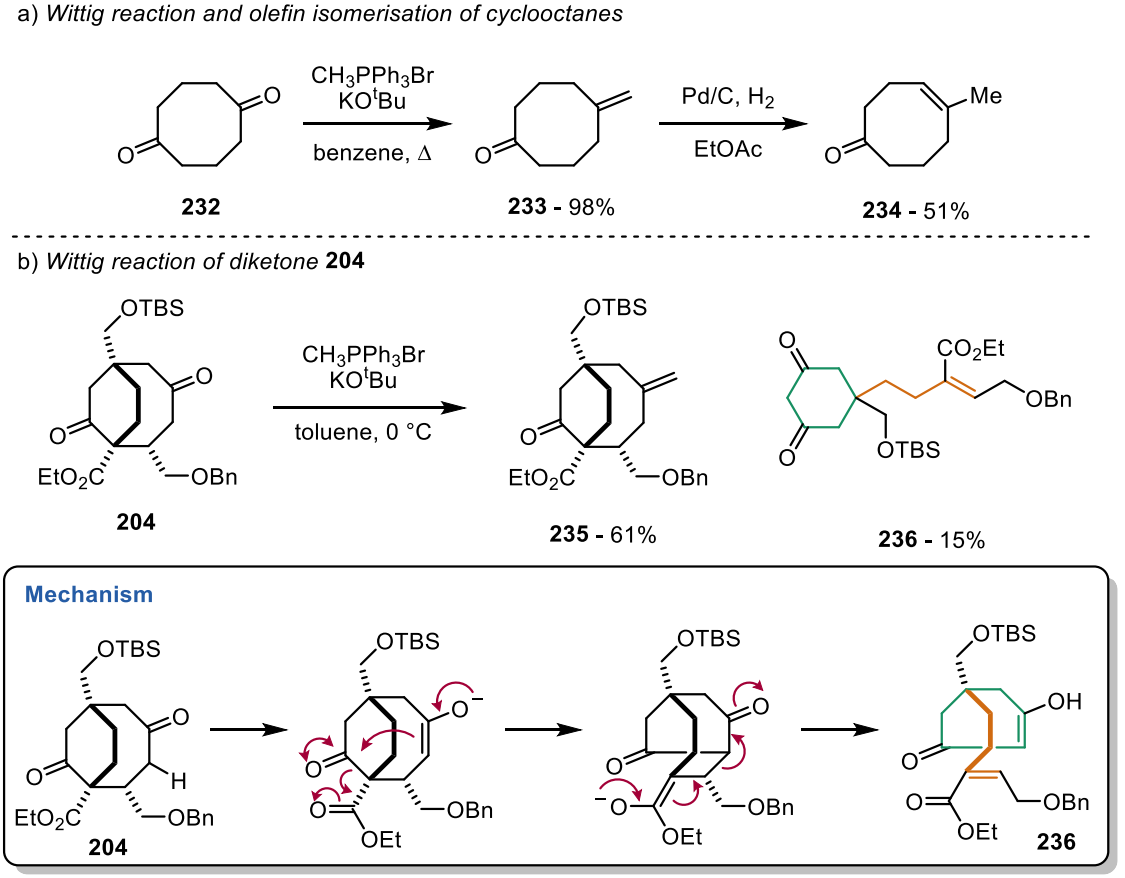
Scheme 104 – [2+2]-Photocycloaddition of **221** to give **229**, followed by formation of **204** through a retro-aldol ring-opening

Based on the model studies, the next step was addition of methyllithium to **204** which resulted in only 18% of the desired product **230** (Scheme 105). In addition, 13% of the transannular acetal **231** was isolated. Repeating the reaction with methylmagnesium bromide returned only starting material.



Scheme 105 – Reaction of **204** with methyllithium to form **230** and **231**

As the regioselective nucleophilic addition to diketone **201** was more successful than regioselective deprotonation, an alternative nucleophilic method for the addition of a methyl group was investigated. Molander *et al.* have shown that Wittig reaction of cyclooctadione **232** gave exocyclic alkene **233** which can then be isomerised under catalytic hydrogenation conditions to afford an internal alkene **234** (Scheme 106a).[200] Nucleophilic addition of a Wittig reagent to **204** should be expected to exhibit the same regioselectivity as observed for methyllithium addition. By-products formed from transannular reactions should also be inhibited as the resulting alkoxide should rapidly react with the phosphonium.



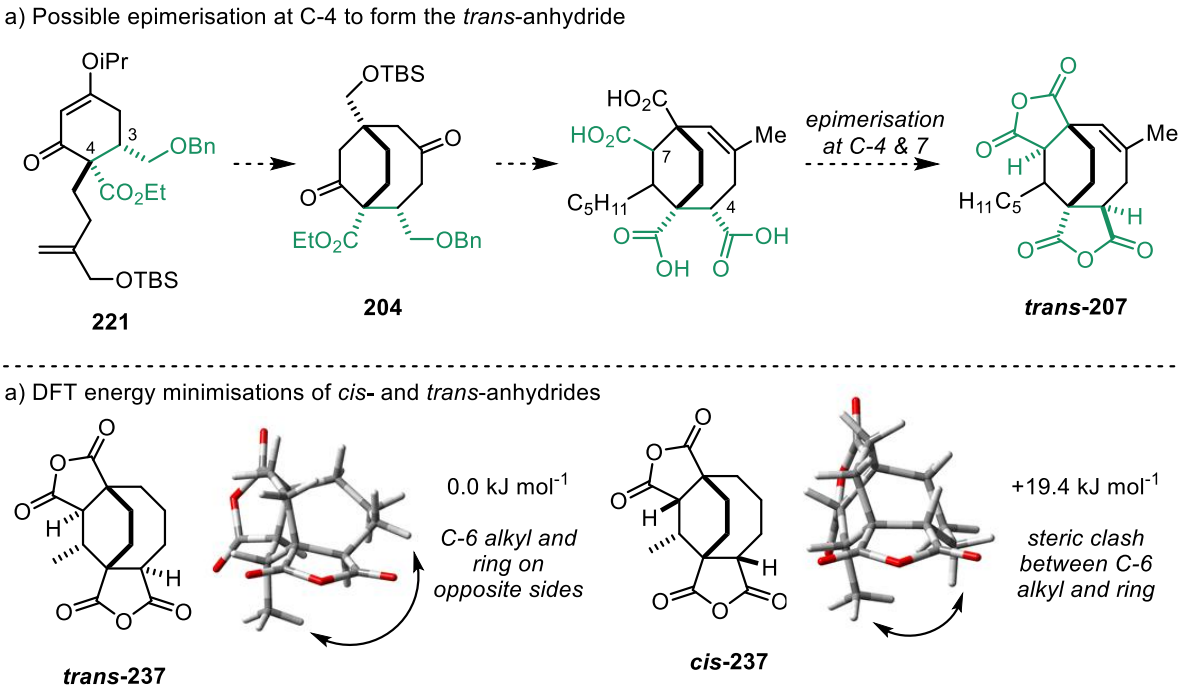
Scheme 106 – Successful Wittig reaction of **204** and mechanism for formation of by-product **236**

Treatment of diketone **204** with methyltriphenylphosphonium bromide gave exocyclic alkene **235** in 61% yield after brief optimisation (Scheme 106b) By-product **236** was also isolated and presumably formed as a result of the basic conditions. Hence in later reactions, formation of

the Wittig reagent was carried out for at least 1 h at 40 °C followed by cooling to 0 °C for addition of **236** to give the optimal 61% yield.

3.3.6.1. Alkylation Stereochemistry

As determined in initial alkylation reactions of **165**, the major product **221** has the 3-ester and 4-benzyloxymethyl groups on the same side. Although the *cis*-diastereoselectivity achieved in these reactions has always been excellent, these moieties will eventually go on to form one of the anhydrides in viburspiran, in which the relationship between them should be *trans*. As one of the final steps in the synthesis, deprotection of the benzyl ether and oxidation followed by ring closure should allow formation of the anhydride rings. It was thought that the acidic/basic conditions necessary to form these groups would also lead to epimerisation at C-4 and therefore provide the desired relative stereochemistry ***trans*-207** (Scheme 107a).



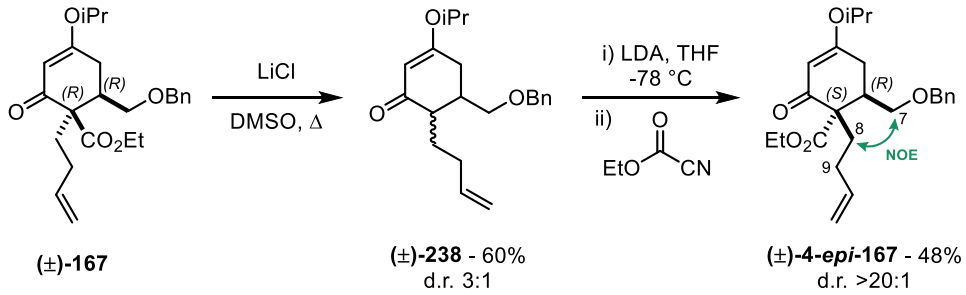
Scheme 107 – a) Proposed epimerisation that could occur upon anhydride formation to give ***trans*-207** b) DFT minimised structures (Gaussian 09, DFT: B3LYP,6-31G)[186] of ***cis*-** and ***trans*-237**

As a basic model for viburspiran, ***trans*-237** (with some functionality omitted for computational simplicity) was subjected to energy minimisation (Gaussian 09, DFT: B3LYP,6-31G)[186] and found to adopt a twisted chair conformation. Minimisation of the lowest energy conformer of ***cis*-237**, in which the stereochemistry at C-4 and C-7 is inverted from the natural viburspiran stereochemistry, was found to exist in a boat-like conformation and consequently had an energy of around 19 kJ mol^{-1} higher than the ***trans*-237** diastereomer. As well as being one of the higher energy conformers for cyclooctanes, steric interaction between the C-6 alkyl and the RHS of the ring also likely increases the energy of this diastereomer. This

indicates that should epimerisation at C-4 and C-7 occur, ring closure to form the trans-anhydrides should give the lowest energy structure.

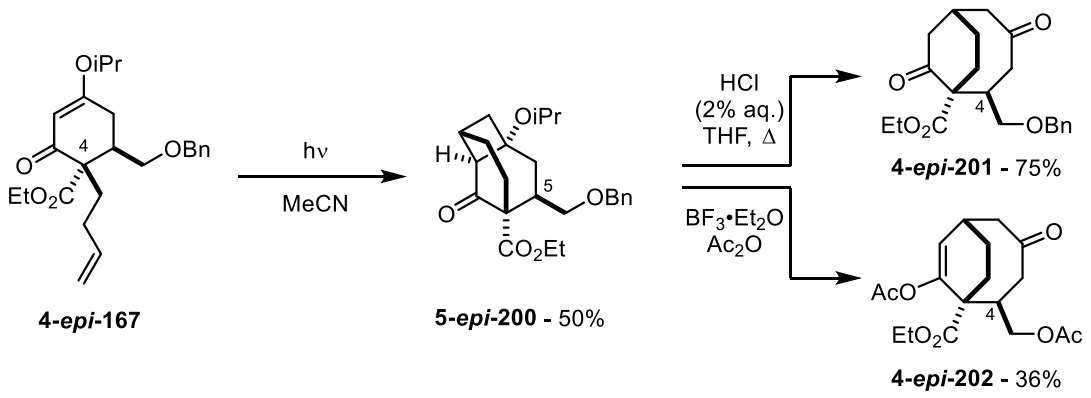
In the event that epimerisation is found to be unsuccessful in forming the desired diastereomer upon anhydride formation, alternative solutions to set this stererochemistry earlier in the synthesis were explored. It was envisaged that if **221** were to undergo decarboxylation, re-carboxylation would occur from the opposite face to the benzyl ether, forming the *trans*-product.

Decarboxylation of **221** was initially attempted by basic hydrolysis of the ethyl ester to the carboxylic acid followed by heating to promote decarboxylation of the β-keto acid. Unfortunately, this method was unsuccessful and only afforded ring opened products resulting from the retro-aldol reaction of the β-keto ester. Instead, Krapcho decarboxylation conditions were used to prevent ring-opening, which led to **238** in a 60% yield as a 3:1 mixture of diastereomers (Scheme 108).[201] Subsequent deprotonation of **238** at the α-position meant that the diastereoselectivity was not an issue, and addition of ethyl cyanoformate led to the re-carboxylated product **4-*epi*-167** in 48% yield and excellent diastereoselectivity. The relative stereochemistry of **4-*epi*-167** was confirmed by NOE NMR, showing a correlation between C-7 and C-8/9 which was not present in **167**.



Scheme 108 – Decarboxylation of **167** and re-carboxylation to invert stereochemistry

4-*epi*-167 was then subjected to the de Mayo reaction under the same conditions as previously to give **5-*epi*-200** in 50% yield (Scheme 109). **5-*epi*-200** was then ring opened under aqueous acidic conditions to give **4-*epi*-201** in 75% yield or alternatively use of a Lewis acid and acetic anhydride gave the enol acetate **4-*epi*-202** in 36% yield. Due to lack of material, the route was not continued further with this stereochemistry, however it was valuable to know that **4-*epi*-167** is able to undergo these transformations.



Scheme 109 – Cyclisation and ring-opening of **4-*epi*-167**

When comparing the ^{1}H-NMR spectra of **201** and **4-*epi*-201**, the signals assigned to H_2-9 were distinctive (Figure 20). In **201**, H_2-9 appeared as a triplet and a doublets of doublets with geminal coupling (J = 9.8 Hz) and vicinal coupling to H_2-4 (J = 9.8 and 3.0 Hz). In **4-*epi*-201** however, the signal assigned to H_2-9 appears as a doublet with only vicinal coupling (J = 6.1 Hz) implying that the protons experience little or no coupling to one-another despite being diastereotopic.

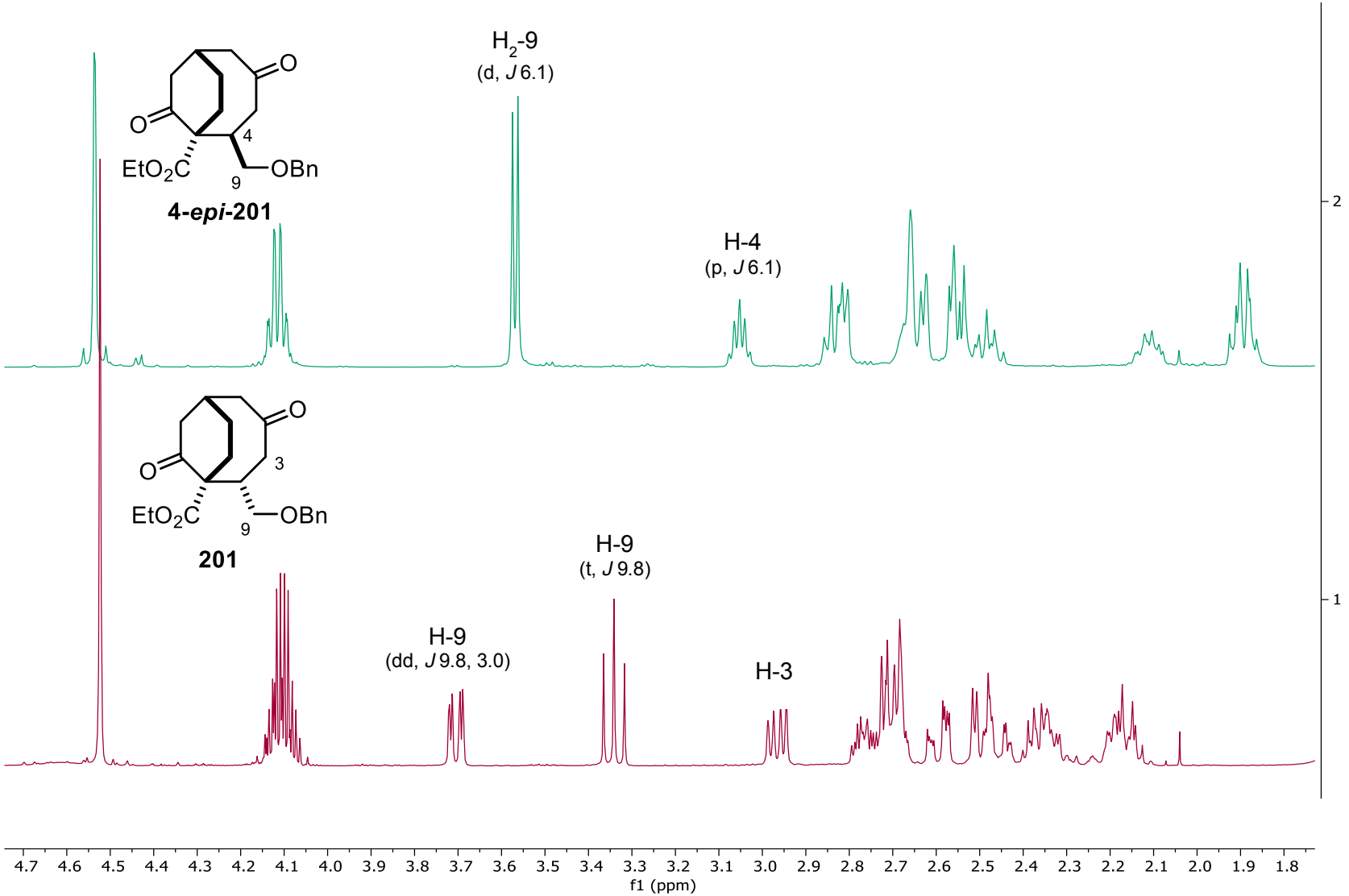
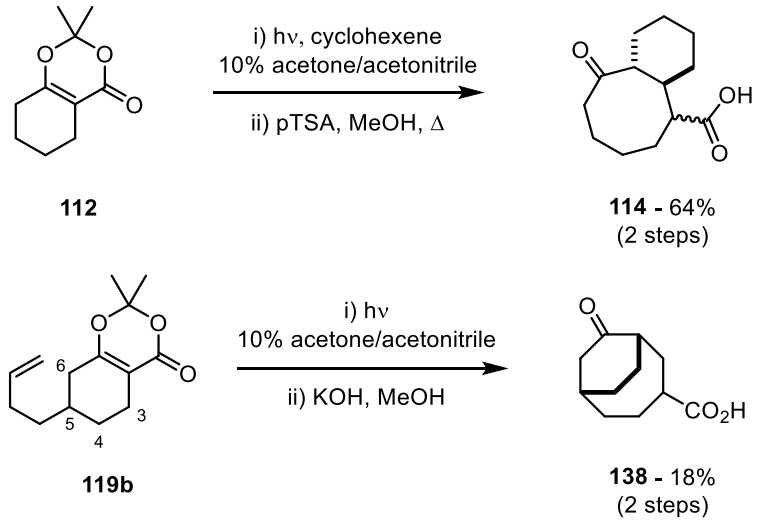


Figure 20 - Comparison of the ^{1}H-NMR spectra of **201** and **4-*epi*-201**

3.4. Conclusions

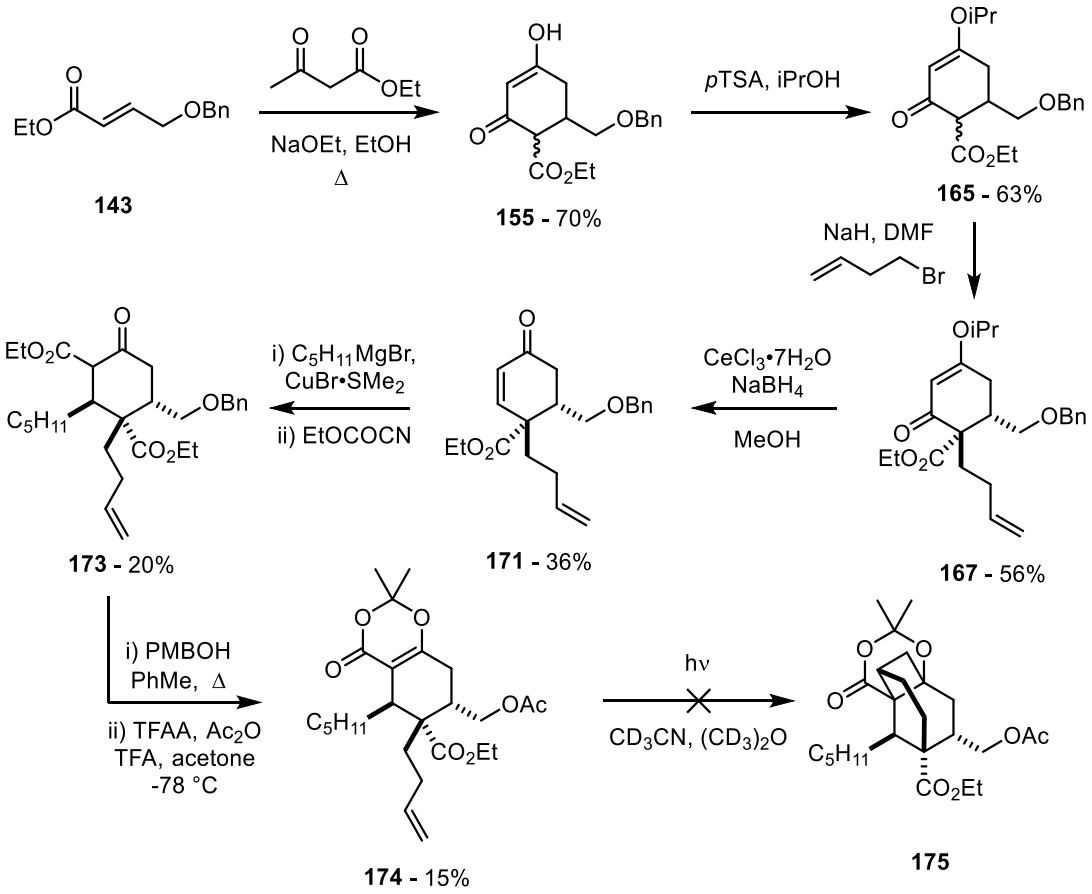
In summary, good progress has been made towards the first total synthesis of the maleidride natural product viburspiran using a de Mayo [2+2]-photocycloaddition-retro aldol reaction as the key step. Initial intramolecular [2+2]-photocycloaddition of model substrate **103** was unsuccessful and the use of either dioxenones or maleimides as a viable alternative chromophore was explored (Section 3.3.1.1 and 3.3.1.2). Dioxenone **112** underwent intermolecular photoaddition with cyclohexene giving **114** in 64% yield, and a suitable intramolecular route was explored (Scheme 110). Three β-ketoester substrates **119a-c** suitable for intramolecular photochemical cycloadditions were synthesised, differing in their substitution pattern, in order to investigate possible routes towards the viburspiran core (Section 3.3.2). **119b** was used in the synthesis of the core carbocyclic structure of viburspiran and gave **138** in 18% yield over 2 steps (Scheme 110). Two other regioisomers with substitution at C-3 (**119d**) and C-6 (**119a**) were found to exhibit no reaction or give the wrong photochemical regioisomer respectively (Section 3.3.3, Scheme 75). The synthesis of **119c** was unfortunately unsuccessful but was predicted to react in a similar manner as **119b**.



Scheme 110 – Inter- and intramolecular dioxenone test reactions for the synthesis of eight-membered carbocycles

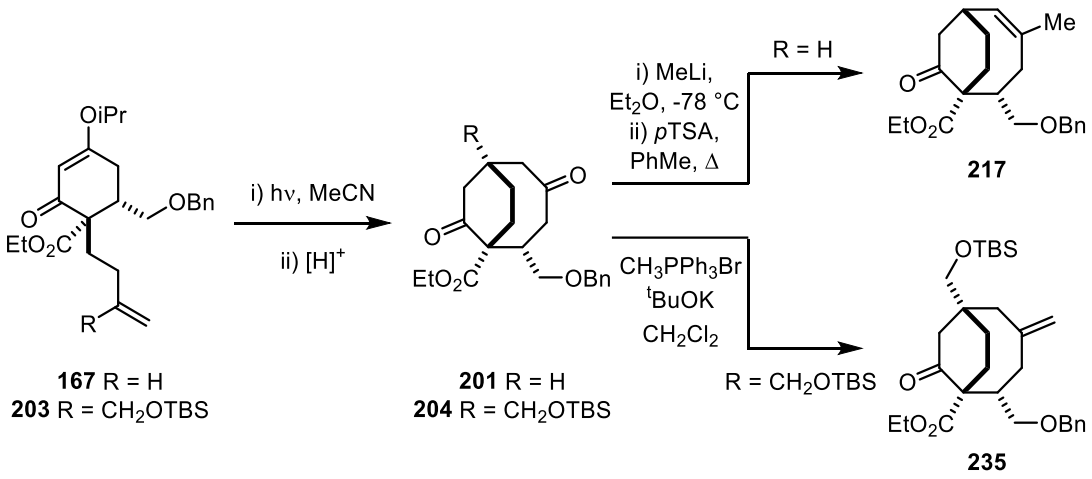
With much of the functionality of viburspiran in place, dioxenone **174** was synthesised in 7 steps (Scheme 111). Unfortunately, photochemical irradiation of **174** was unsuccessful, and DFT optimisation of the possible conformers of the simplified model structure **176** revealed that the optimum geometry of **174** may disfavour reaction of the alkene tether with the dioxenone (Section 3.3.4, Scheme 85). After reconsideration of the total synthesis, **167** was identified as an alternative substrate for [2+2]-cyclisation (Scheme 112). **167** successfully

underwent the desired transformation to give **201** in excellent yield, and the route was redesigned around this successful result (Section 3.3.6).



Scheme 111 – Summary of the route to dioxenone **174** in 7 steps

After successful cyclisation of **167** to give the diketone **201**, methods for the functionalisation of the LHS and RHS of the molecule were investigated. Selective deprotonation of **201** at C-7 gave a complex mixture of products under most conditions. Regioselective reaction of diketone **201** with a nucleophile was more successful and allowed synthesis of the tertiary alcohol followed by elimination to the alkene **217** (Scheme 112). Elimination was found to be selective and this work was also backed up by preliminary DFT studies used to accurately predict the lowest energy product of this reaction (Section 3.3.6, Scheme 99).



Scheme 112 – Key de Mayo reaction and subsequent methylation-elimination or methylenation to give **217** and **235**

Synthesis of a substituted alkylating agent **193** was also carried out and the optimal route was found to begin with reduction of dimethyl itaconate with DIBAL-H, followed by mono-TBS protection and an Appel reaction to install the iodide (Section 3.3.5, Scheme 91). After some optimisation, successful conditions for alkylation of **165** with **193** were identified and led to synthesis of the key diketone product **204**. Nucleophilic addition of a methyl group to **204** was unfortunately low-yielding and accompanied by a significant amount of by-product formation. However, it was instead found that Wittig reaction of **204** proceeded regioselectively in 61% yield to give **235** (Scheme 112).

Overall progress has been made towards the total synthesis of maleidride natural product viburspiran using a key photochemical step. Synthesis of the core carbocyclic structure has been carried out and optimised to allow easy access to functionalised [2.2.4]-decacyclic molecules that will facilitate further transformations towards the natural product.

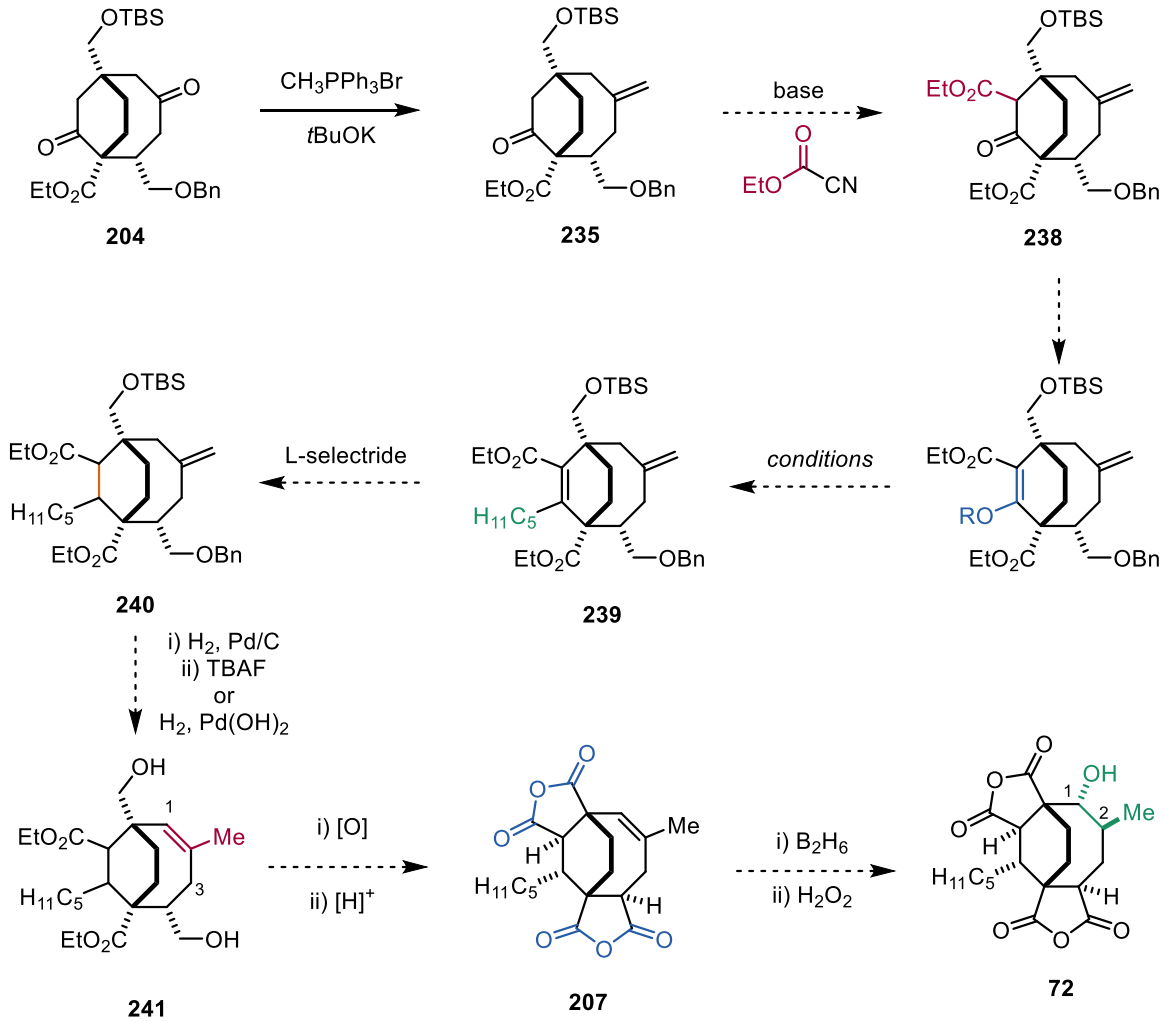
3.5. Future Work

Future work on this project will involve completion of the total synthesis based on the route established in this thesis. Following synthesis of **235** by selective Wittig reaction, functionalisation of the LHS will be necessary to install the C-7 carboxyl and C-6 pentyl units followed by formation of the anhydrides, and finally installation of the 2-hydroxy group through hydroboration-oxidation (Scheme 113).

The presence of a single acidic site on **235** should allow easy deprotonation and carboxylation using ethyl cyanoformate or similar, to give **238**. Incorporation of the *n*-pentyl chain at C-5 could be achieved in several ways. Published methods include the reaction of enol pivalates with Grignard reagents in the presence of $FeCl_2$ and LiCl;[202] reaction of enol acetates with Grignard reagents in the presence of catalytic $FeCl_2$ and NMP;[203] and reaction of enol triflates

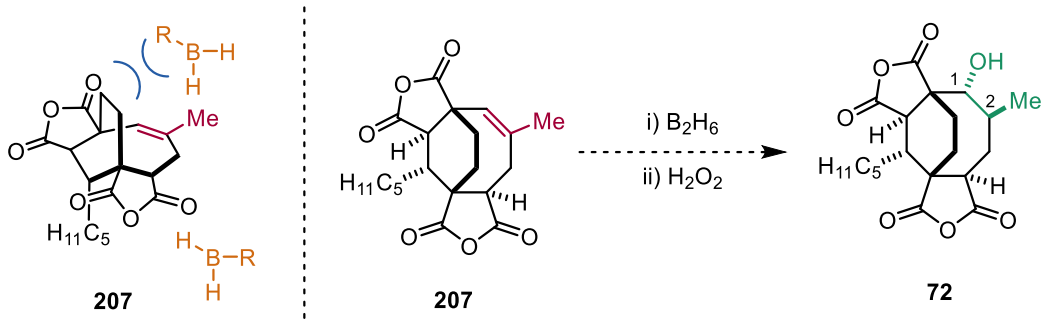
with organocuprates.[204] Most of these methods have been widely used giving several options to achieve this step and form **239** successfully.

Following incorporation of the *n*-pentyl chain, reduction of the α,β-unsaturated ester to give **240**, deprotection of the benzyl and TBS groups and isomerisation of the exocyclic methylene to give **241** need to be carried out. Deprotection of the benzyl ether and TBS group may be carried out in one step[205] by hydrogenolysis in the presence of $Pd(OH)_2$, or alternatively could be carried out in two steps by hydrogenation followed by TBAF deprotection. Using either of these methods, the hydrogenation conditions could also allow reduction of the α,β-unsaturated ester and cause isomerisation of the exocyclic methylene to the internal alkene based on a similar literature procedure (Scheme 106a).[200] DFT calculations carried out (Scheme 99) also indicate that the C-1 alkene should be thermodynamically favoured over the C-3 alkene. If the α,β-unsaturated ester is not able to be reduced by hydrogenolysis, L-selectride could be used to achieve this first, followed by the deprotection and isomerisation steps to give **241** (Scheme 113).



Scheme 113 – Proposed steps for completion of the total synthesis of (±)-viburspuiran from **235**

The penultimate step in the synthesis will involve formation of the anhydride units through oxidation of the alcohols. White *et al.* have demonstrated a similar process in the final step of the synthesis of (±)-byssochlamic acid, where they found that aqueous basic hydrolysis of the ester followed by permanganate oxidation allowed formation of the maleic anhydride units from the butenolide.[133] Using the same conditions, the ester units could be hydrolysed to the carboxylic acids, followed by oxidation of the alcohols to the respective carboxylic acids, and finally an acidic workup to form the anhydride units to give **207**. Multiple reaction conditions could be used for the oxidation including the permanganate conditions used by White *et al.*,[133] or if necessary a milder approach of DMP oxidation to the aldehyde, followed by a Pinnick oxidation could be attempted.



Scheme 114 – 3-Dimensional representation of **207** demonstrating the stereochemical effect steric-hinderance from the ethylene bridge could have on hydroboration

The final step in the synthesis is proposed to be hydroboration-oxidation to install the secondary alcohol at C-1. Making this the final step means that the resulting alcohol there are no selectivity issues in the formation of the anhydrides. Based on three-dimensional representations of **207**, hydroboration from the bottom face seems more favourable as it would avoid interaction with the ethylene bridge (Scheme 114). Similar diastereoselectivity has been observed in the hydroboration-oxidation of functionalised medium-sized rings where hydroboration occurs from the least hindered face.[206,207] Borane THF complex is most commonly used for this transformation but bulkier boranes such as 9-BBN could be used to enhance selectivity if necessary. Oxidation of the alkyl borane with hydrogen peroxide should then allow transformation to (±)-viburspiran to complete the total synthesis.

Chapter 4: Experimental

4. Experimental

4.1. General Information

All reactions were carried out under an inert atmosphere using Schlenk like techniques and flame-dried glassware unless otherwise stated. Reaction temperatures at -78 °C were achieved with a dry ice and acetone bath. CH_2Cl_2, and THF and MeCN were collected from a Grubbs type solvent purification system. Solvents used for photochemical reactions were degassed prior to use by subjecting them to vacuum. Other commercial reagents were used as supplied unless otherwise stated. Flash chromatography was performed using silica gel 60 (Fisher Scientific or Sigma Aldrich) and a suitable eluent. Analytical TLC was carried out on pre-coated UV-254 plates, with visualisation by UV light at 254 nm and potassium permanganate dip.

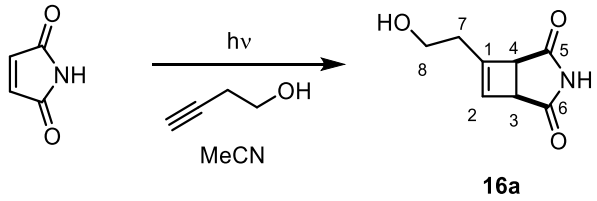
^{1}H and ^{13}C NMR spectra were recorded at ambient temperature unless otherwise stated on Jeol ECP (Eclipse) 300, Jeol ECS 300, Jeol ECS 400, Varian 400-MR, Varian VNMRS 500 spectrometers and a Bruker Advance III HD 500 spectrometer equipped with a ^{13}C-observe (DCH) cryogenic probe. Chemical shifts δ are given in parts per million (ppm) and referenced to the appropriate solvent peak(s) (δ H: $CDCl_3$ 7.26 ppm, D_2O 4.79 ppm, CD_3OD 3.31 ppm, δ C: $CDCl_3$ 77.0 ppm, CD_3OD 49.0 ppm,) and coupling constants J are in Hz. In instances of ambiguity, mean J values have been quoted, rounded to the nearest decimal point. For simplicity, in some cases, the numbering system used for ^{1}H-NMR assignment does not reflect IUPAC name and numbering system.

Mass Spectra were recorded by the University of Bristol Mass Spectrometry Service on a VG Analytical Autospec (EI) or VG Analytical Quattro (ESI) spectrometer. Melting points were measured on a Kofler Hotstage melting point apparatus and are uncorrected. IR spectra were recorded on neat compounds using a Perkin Elmer (Spectrum One) FT-IR spectrometer (ATR sampling accessory). Only selected absorbance's (υ_{max} expressed in cm^{-1}) are reported.

Photochemical reactions were carried out in a Pyrex 150 mL batch reactor with a medium pressure 125 W mercury lamp under nitrogen. The reaction vessel was wrapped in aluminium foil to reduce risk of exposure and maximise internal reflection.

4.2. Experimental Procedures for Chapter 2

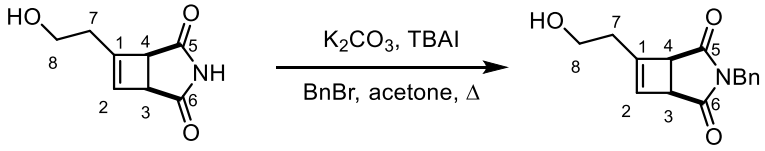
16a – (±)-6-(2-Hydroxyethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione



16a

Maleimide (1.46 g, 15.0 mmol) and but-3-yn-1-ol (1.70 mL, 22.5 mmol) were dissolved in degassed acetonitrile (150 mL) and irradiated for 3 h. After this time the solvent was removed under reduced pressure to yield the crude product as an off-white residue. The product was purified by column chromatography (80-100% ethyl acetate/petroleum ether) giving **16a** (1.54 g, 61%) as a white solid; **m.p.** (acetonitrile) 114-116 °C; **IR** υ_{max}/cm^{-1} 3197, 1762, 1699, 1669; **^{1}H NMR** (400 MHz, D_2O) δ 6.28 (*app.* q, *J* 1.5, 1H, *H*-2), 3.91 (m, 1H, *H*-4), 3.83 – 3.73 (m, 3H, *H*-8 & *H*-3) 2.51 – 2.41 (m, 2H, *H*-7); **^{13}C NMR** (101 MHz, D_2O) δ 180.5 (*C*-5/6), 179.6 (*C*-5/6), 150.5 (*C*-1), 131.4 (*C*-2), 58.4 (*C*-8), 50.1 (*C*-4), 45.8 (*C*-3), 32.2 (*C*-7); **HRMS** (ESI^+) 190.0475 $[M + Na]^+$ ($C_8H_9NNaO_3$ requires 190.0481). Data in accordance with literature.[208]

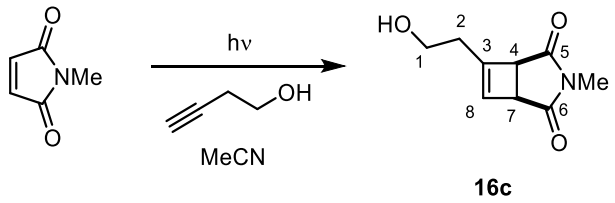
16b – (±)-3-Benzyl-6-(2-hydroxyethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione



16a **16b**

16a (1.54 g, 9.2 mmol), potassium carbonate (1.91 g, 13.8 mmol) and tetrabutylammonium iodide (0.17 g, 0.46 mmol) were dissolved in acetone (20 mL). Benzyl bromide (1.2 mL, 10.1 mmol) was added, and the solution heated at reflux. After 4 h at reflux the reaction mixture was cooled to room temperature to give a pale pink suspension. The solids were removed by filtration and the filtrate concentrated under reduced pressure to give the crude product as an orange oil. The product was purified by column chromatography (5% diethyl ether/DCM) to give the pure product **16b** (1.77 g, 75%) as an off white solid; **m.p.** (acetonitrile) 76-77 °C; **IR** υ_{max}/cm^{-1} 3345, 1764, 1693; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.15 (m, 5H, C*H* arom.), 6.13 (s, 1H, *H*-2), 4.57 (s, 2H, PhCH_2) 3.81 – 3.57 (m, 4H, *H*-8, *H*-4 and *H*-3), 2.78 (t, *J* 5.4, 1H, -O*H*), 2.37 (t, *J* 6.0, 2H, *H*-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.4 (*C*-5/6), 175.0 (*C*-5/6), 151.2 (*C*-1), 135.7 (*C* arom.), 131.4 (*C*-2), 128.6 (*C*H arom.), 128.3 (*C*H arom.), 127.8 (*C*H arom.), 59.5 (*C*-8), 48.6 (*C*-4), 44.4 (*C*-3), 42.1 (Ph*C*H_2), 33.3 (*C*-7); **HRMS** (ESI^+) 280.0942 $[M + Na]^+$ ($C_{15}H_{15}NNaO_3$ requires 280.0944).

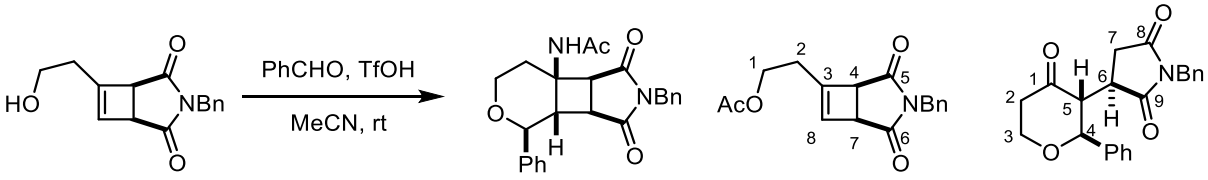
16c – (±)-6-(2-Hydroxyethyl)-3-methyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione



16c

N-methylmaleimide (1.68 g, 15 mmol) and 3-butyn-1-ol (1.70 mL, 22.5 mmol) were dissolved in degassed acetonitrile (150 mL) and irradiated with a 125 W UV lamp. After 5 h, the solvent was removed under reduced pressure and the crude product purified by column chromatography (50% ethyl acetate/petroleum ether) to give the pure product **16c** (1.26 g, 46%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3440 (br), 2949, 1764, 1683; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.17 (m, 1H, *H*-8), 3.85 – 3.70 (m, 3H, *H*-1 & *H*-4), 3.66 (m, 1H, *H*-7), 2.94 (s, 3H, C*H*$_3$), 2.57 – 2.33 (m, 2H, *H*-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8 (*C*=O), 175.4 (*C*=O), 151.2 (*C*-3), 131.4 (*C*-8), 59.5 (*C*-1), 48.6 (*C*-4), 44.4 (*C*-7), 33.3 (*C*-2), 24.9 (*C*H$_3$); **HRMS** (ESI^+) 204.0638 $[M + Na]^+$ ($C_9H_{11}NNaO_3$ requires 204.0631).

23 and 24 – (±)-2-(3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)ethyl acetate and (±)-1-benzyl-3-(4-oxo-2-phenyltetrahydro-2H-pyran-3-yl)pyrrolidine-2,5-dione



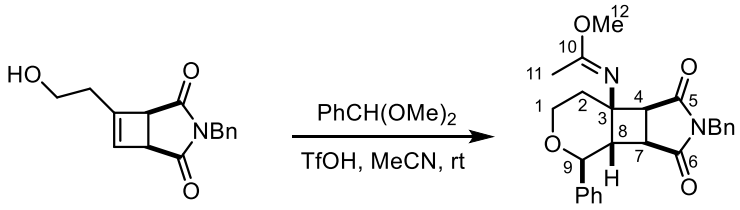
16b **22b** **23** **24**

Homoallylic alcohol **16b** (1.00 g, 3.89 mmol) and benzaldehyde (0.40 mL, 3.89 mmol) were dissolved in anhydrous acetonitrile (20 mL) and trifluoromethanesulfonic acid (0.41 mL, 4.67 mmol) added dropwise at room temperature. After 30 min, the reaction was quenched with water (10 mL) before extracting with ethyl acetate (3 × 10 mL). The combined organic layers were washed with sodium hydrogen carbonate, dried with magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield the crude product which was purified by column chromatography (50-75% ethyl acetate/petroleum ether) to give the products **22b** (49%), **23** (17%) and **24** (17%). **23 - IR** υ_{max}/cm^{-1} 2966, 1766, 1736, 1695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H, C*H arom.*), 6.16 (m, 1H, *H*-8), 4.59 (s, 2H, PhC*H*$_2$), 4.22 (dt, *J* 11.0, 6.4, 1H, *H*-1), 4.12 (dt, *J* 11.0, 6.4, 1H, *H*-1), 3.72 (m, 1H, *H*-4/7), 3.63 (m, 1H, *H*-4/7), 2.52 – 2.43 (m, 2H, *H*-2), 1.99 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.8 (*C*=O), 174.0 (*C*=O), 170.8 (*C*=O), 149.9 (*C*-3), 135.8 (*C* arom.), 135.7 (*C* arom.), 131.8 (*C*-8), 129.3 (*C*H arom.), 128.6 (*C*H arom.), 128.5 (*C*H arom.), 127.8 (*C*H arom.), 60.9 (*C*-1), 48.7 (*C*-4), 44.3

(*C*-7), 42.1 (Ph*C*H$_2$), 29.3 (*C*-2), 20.8 (*C*H$_3$); **HRMS** (ESI$^+$) 300.1238 [M+H]$^+$, 322.1063 [M + Na]$^+$ ($C_{17}H_{18}NO_4$ requires 300.1230, $C_{17}H_{17}NNaO_4$ requires 322.1050); **24 - m.p.** (methanol) 159-161 °C; **IR** υ_{max}/cm^{-1} 2950, 1766, 1700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.05 (m, 10H, C*H* arom.), 4.58 (d, *J* 14.4, 1H, PhC*H*$_2$), 4.49 (d, *J* 14.4, 1H, PhC*H*$_2$), 4.30 (ddd, *J* 11.7, 7.6, 1.2, 1H, *H*-3), 4.22 (d, *J* 10.8, 1H, *H*-4), 3.70 (ddd, *J* 12.8, 11.7, 2.6, 1H, *H*-3), 3.40 (ddd, *J* 10.8, 3.5, 1.2, 1H, *H*-5), 2.76 (dddd, *J* 14.4, 12.8, 7.6, 1.2, 1H, *H*-2), 2.47 (d, *J* 8.7, 1H, *H*-7), 2.45 (d, *J* 7.0, 1H, *H*-7), 2.34 (ddd, *J* 14.4, 2.6, 1.2, 1H, *H*-2) 2.17 (ddd, *J* 8.7, 7.0, 3.5, 1H, *H*-6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.1 (*C*-1), 178.2 (*C*-9), 175.5 (*C*-8), 137.9 (*C* arom.), 135.7 (*C* arom.), 129.4 (*C*H arom.), 129.2 (*C*H arom.), 128.5 (*C*H arom.), 127.7 (*C*H arom.), 126.8 (*C*H arom.), 83.6 (*C*-4), 67.2 (*C*-3), 56.9 (*C*-5), 42.5 (Ph*C*H$_2$), 42.4 (*C*-2), 37.3 (*C*-6), 31.3 (*C*-7); **HRMS** (ESI$^+$) 386.1354 [M + Na]$^+$ ($C_{22}H_{21}NNaO_4$ requires 386.1368).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8, 131.8, 129.3, 128.6, 128.5, 127.8

25 – (±)-Methyl(*E*)-*N*-(2-benzyl-1,3-dioxo-4-phenyloctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetimidate

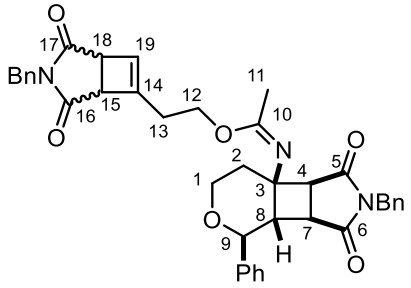


16b **25**

16b (1.00 g, 3.90 mmol) and benzaldehyde dimethylacetal (0.70 mL, 4.70 mmol) were dissolved in anhydrous acetonitrile (20 mL) and trifluoromethanesulfonic acid (0.52 mL, 5.80 mmol) was added dropwise at room temperature. After 18 h, the reaction was quenched with saturated aqueous sodium hydrogen carbonate solution (3.0 mL) and extracted with DCM (3 × 10 mL). The organic layers were combined and dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The resulting crude product was purified by trituration with hexane to give **25** (0.48 g, 29%) as a colourless solid; **m.p.** (hexane) 135-137 °C; **IR** υ_{max}/cm^{-1} 2965, 1763, 1694, 1672; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.67 – 7.50 (m, 2H, C*H* arom.), 7.44 – 7.17 (m, 8H, C*H* arom.), 4.85 (d, *J* 5.0, 1H, *H*-9), 4.66 (s, 2H, PhC*H*$_2$), 3.88 (ddd, *J* 11.8, 7.7, 4.5, 1H, *H*-1), 3.70 (ddd, *J* 11.8, 6.8, 4.5, 1H, *H*-1), 3.56 (d, *J* 6.5, 1H, *H*-4), 3.49 (s, 3H, OC*H*$_3$), 3.20 (dd, *J* 6.5, 5.0, 1H, *H*-7), 2.92 (t, *J* 5.0, 1H, *H*-8), 2.20 (ddd, *J* 14.4, 7.7, 4.5, 1H, *H*-2), 2.02 (s, 3H, *H*-11), 1.92 (ddd, *J* 14.4, 6.8, 4.5, 1H, *H*-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.9 (*C*-6), 175.2 (*C*-5), 163.1 (*C*-10), 140.6 (*C* arom.), 135.9 (*C* arom.), 128.6 (*C*H arom.), 128.4 (*C*H arom.), 127.8 (*C*H arom.), 127.8 (*C*H arom.), 127.3 (*C*H arom.), 78.9 (*C*-9),

60.4 (*C*-1), 56.7 (*C*-3), 52.7 (OC*H*$_3$), 50.3 (*C*-8), 49.7 (*C*-4), 42.4 (Ph*C*H$_2$), 39.5 (*C*-7), 35.3 (*C*-2), 19.0 (*C*-11); **HRMS** (ESI$^+$) 441.1766 [M + Na]$^+$ ($C_{25}H_{26}N_2NaO_4$ requires 441.1785).

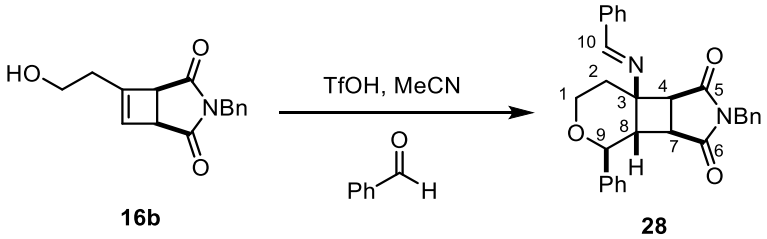
27 – (±)-3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)ethyl(*Z*)-*N*-(2-benzyl-1,3-dioxo-4-phenyloctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetimidate



27

Reaction conducted according to general procedure A (see Section 4.2.1), product purified using automated column chromatography (CombiFlash, 60-100% TBME/isohexanes) to give **27** as a colourless solid (1:1 mixture of diastereomers); **IR** υ_{max}/cm^{-1} 2932, 1763, 1686; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 4H, C*H* arom.), 7.45 – 7.18 (m, 26H, C*H* arom.), 6.13 (q, *J* 1.5, 1H, *H*-19), 6.11 (q, *J* 1.5, 1H, *H*-19), 4.86 – 4.81 (m, 2H, 2 × *H*-9), 4.64 – 4.57 (m, 8H, 4 × PhC*H*$_2$), 4.04 (*app.* dt, *J* 10.9, 6.3, 1H, *H*-12), 3.99 (ddd, *J* 10.9, 7.1, 5.7, 1H, *H*-12), 3.95 (*app.* dt, *J* 10.9, 6.1, 1H, *H*-12), 3.87 – 3.76 (m, 3H, *H*-12 & 2 × *H*-1), 3.76 – 3.60 (m, 6H, 2 × *H*-1, 2 × *H*-15 & 2 × *H*-18), 3.56 – 3.49 (m, 2H, 2 × *H*-4), 3.22 – 3.14 (m, 2H, 2 × *H*-7), 2.92 – 2.85 (m, 2H, 2 × *H*-8), 2.45 – 2.38 (m, 4H, 2 × *H*-13), 2.22 – 2.13 (m, 2H, 2 × *H*-2), 1.97 (s, 3H, *H*-11), 1.93 (s, 3H, *H*-11), 1.92 – 1.84 (m, 2H, 2 × *H*-2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.9 (*C*-6), 177.8 (*C*-6), 175.5 (2 × *C*-16/17), 175.1 (2 × *C*-5), 174.1 (2 × *C*-16/17), 162.5 (*C*-10), 162.4 (*C*-10), 150.9 (*C*-14), 150.8 (*C*-14), 140.6 (2 × *C* arom.), 135.9 (2 × *C* arom.), 131.5 (2 × *C* arom.), 131.2 (2 × *C*-19), 128.7 (*C*H arom.), 128.6 (*C*H arom.), 128.5 (*C*H arom.), 128.4 (*C*H arom.), 127.9 (*C*H arom.), 127.8 (*C*H arom.), 127.3 (*C*H arom.), 127.2 (*C*H arom.), 78.6 (*C*-9), 78.4 (*C*-9), 61.8 (*C*-12), 61.7 (*C*-12), 60.3 (*C*-1), 60.2 (*C*-1), 59.6, 56.6 (*C*-3), 56.5 (*C*-3), 50.3 (2 × *C*-8), 49.7 (2 × *C*-4), 48.8 (*C*-15), 48.7 (*C*-15), 48.6, 44.4 (2 × *C*-18), 42.5 (Ph*C*H$_2$), 42.4 (Ph*C*H$_2$), 42.2 (Ph*C*H$_2$), 42.1 (Ph*C*H$_2$), 39.4 (*C*-7), 39.3 (*C*-7), 35.3 (*C*-2), 35.2 (*C*-2), 29.1 (*C*-13), 29.0 (*C*-13), 19.2 (*C*-11), 19.1 (*C*-11); **HRMS** (ESI$^+$) 644.2775 [M+H]$^+$ ($C_{39}H_{38}N_3O_6$ requires 644.2755).

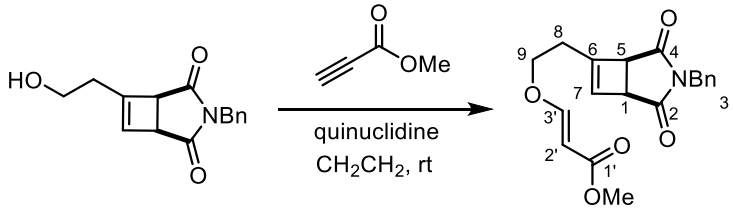
28 – (±)-2-Benzyl-7a-(((*E*)-benzylidene)amino)-4-phenylhexahydropyrano[3',4':3,4]cyclobuta[1,2-c]-pyrrole-1,3(2H,3aH)-dione



16b **28**

28 was isolated in various reactions from the Design of Experiments reactions (e.g. Table 11, Design 1, entry 9, 32%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3032 (w), 2972 (w), 1774 (w), 1698, 1401, 1170, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (s, 1H, *H*-10), 7.65 – 7.58 (m, 2H, C*H* arom.), 7.47 – 7.20 (m, 13H, C*H* arom.), 4.92 (d, *J* 6.7, 1H, *H*-9), 4.67 (d, *J* 14.0, 1H, PhCH_2), 4.54 (d, *J* 14.0, 1H, PhCH_2), 4.10 (m, 1H, *H*-1), 3.98 (ddd, *J* 11.3, 8.2, 5.4, 1H, *H*-1), 3.71 (dd, *J* 6.5, 1.0, 1H, *H*-4), 3.27 (dd, *J* 6.5, 4.4, 1H, *H*-7), 2.99 (dd, *J* 6.7, 4.4, 1H, *H*-8), 2.37 (ddd, *J* 14.1, 8.2, 5.6, 1H, *H*-2), 2.04 (m, 1H, *H*-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.5 (*C*-6), 174.7 (*C*-5), 160.3 (*C*-10), 140.7 (*C* arom.), 135.7 (*C* arom.), 135.6 (*C* arom.), 129.2 (*C*H arom.), 128.7 (*C*H arom.), 128.6 (*C*H arom.), 128.5 (*C*H arom.), 128.4 (*C*H arom.), 128.4 (*C*H arom.), 127.9 (*C*H arom.), 127.7 (*C*H arom.), 125.9 (*C*H arom.), 76.5 (*C*-9), 62.6 (*C*-3), 61.2 (*C*-1), 50.3 (*C*-4), 48.8 (*C*-8), 42.4 (Ph*C*H_2), 39.0 (*C*-7), 32.7 (*C*-2); **HRMS** (ESI^+) 451.2019 $[M+H]^+$ ($C_{29}H_{27}N_2O_3$ requires 451.2016), 473.1834 $[M+Na]^+$ ($C_{29}H_{26}N_2NaO_3$ requires 473.1836).

32 – (±)-Methyl (*E*)-3-(2-(3-benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)ethoxy)acrylate

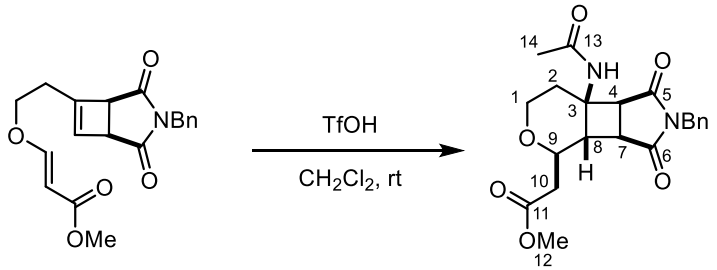


16b **32**

16b (0.20 g, 0.78 mmol) and quinuclidine (2.6 mg, 0.02 mmol) were dissolved in dry DCM (2.0 mL). A solution of methyl propiolate (0.10 mL, 1.2 mmol) in dry DCM (4.0 mL) was added dropwise and the solution stirred at room temperature for 30 min. The reaction was quenched with 5% acetic acid (3 mL) before extracting with DCM (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give the crude product as a brown residue. The product was purified by column chromatography (25% ethyl acetate/petroleum ether) to give the pure product **32** (0.20 g, 76%) as a colourless oil; **IR** υ_{max}/cm^{-1} 1766, 1698, 1624; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* 12.7, 1H, *H*-3'), 7.32 – 7.24 (m, 5H, C*H* arom.), 6.19 (s, 1H, *H*-7), 5.15 (d, *J* 12.7, 1H,

H-2'), 4.61 (d, *J* 14.5, 1H, N-C*H*$_2$), 4.57 (d, *J* 14.5, 1H, N-C*H*$_2$), 3.98 – 3.85 (m, 2H, *H*-9), 3.71 (d, *J* 3.1, 1H, *H*-5), 3.70 (s, 3H, -C*H*$_3$), 3.66 (m, 1H, *H*-1), 2.56 (t, *J* 6.4, 2H, *H*-8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.7 (*C*-2/4), 174.1 (*C*-2/4), 168.1 (*C*-1'), 161.81 (*C*-3'), 149.1 (*C*-6), 135.7 (*C* arom.), 132.4 (*C*-7), 128.6 (*C*H arom.), 128.5 (*C*H arom.), 127.9 (*C*H arom.), 96.7 (*C*-2'), 67.0 (*C*-9), 51.2 (*C*H$_3$), 48.6 (*C*-5), 44.3 (*C*-1), 42.1 (N-*C*H$_2$-), 29.5 (*C*-8); **HRMS** (ESI$^+$) 364.1166 $[M + Na]^+$ ($C_{19}H_{19}NNaO_5$ requires 364.1155).

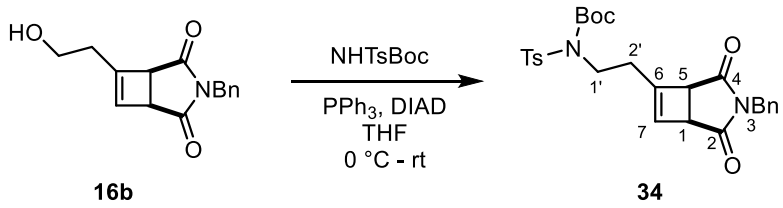
33 – (±)-Methyl 2-(7a-acetamido-2-benzyl-1,3-dioxodecahydropyrano[3',4':3,4]cyclobuta[1,2-c]-pyrrol-4-yl)acetate



32 **33**

32 (100 mg, 0.29 mmol) was dissolved in dry DCM (1.5 mL) and dry acetonitrile (2.5 mL). Trifluorosulfonic acid (60 mg, 40 µL, 0.44 mmol) was added dropwise at room temperature and the reaction mixture left to stir for 30 min. The reaction was then quenched with aqueous sodium hydrogen carbonate solution (3 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were dried with magnesium sulfate, filtered, and the solvent removed under reduced pressure to give the crude product. The crude product was purified by column chromatography (80-100% ethyl acetate/petroleum ether) to give the pure product **33** (55 mg, 48%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3357, 1771, 1734, 1699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H, C*H* arom.), 7.33 – 7.20 (m, 3H, C*H* arom.), 5.60 (s, 1H, N*H*), 4.65 (s, 2H, N-C*H*$_2$), 4.21 (dt, *J* 8.0, 5.8, 1H, *H*-9), 3.95 – 3.83 (m, 2H, *H*-1), 3.70 (s, 3H, *H*-12), 3.31 (d, *J* 6.6, 1H, *H*-4), 3.06 (dd, *J* 6.6, 5.8, 1H, *H*-7), 2.73 (t, *J* 5.8, 1H, *H*-8), 2.68 (dd, *J* 15.5, 8.0, 1H, *H*-10), 2.60 (dd, *J* 15.5, 5.8, 1H, *H*-10), 2.43 (dt, *J* 14.8, 4.4, 1H, *H*-2), 2.04 (ddd, *J* 14.8, 9.5, 6.9, 1H, *H*-2), 1.81 (s, 3H, *H*-14); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (*C*-6), 174.7 (*C*-5), 171.1 (*C*-13), 170.4 (*C*-11), 135.85 (*C* arom.), 128.72 (*C*H arom.), 128.62 (*C*H arom.), 127.93 (*C*H arom.), 70.8 (*C*-9), 60.2 (*C*-1), 52.1 (*C*-3), 51.9 (*C*-12), 48.3 (*C*-4), 46.0 (*C*-8), 42.8 (N-*C*H$_2$), 39.2 (*C*-10), 38.7 (*C*-7), 31.1 (*C*-2), 23.5 (*C*-14); **HRMS** (ESI$^+$) 401.1705 $[M + H]^+$ 423.1532 $[M + Na]^+$ ($C_{21}H_{25}N_2O_6$ requires 401.1707, $C_{21}H_{24}N_2NaO_6$ requires 423.1527).

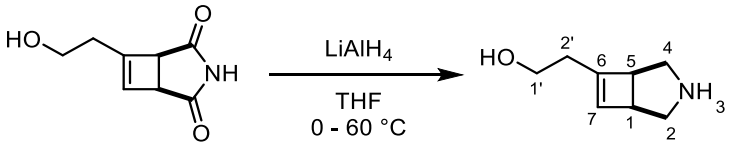
34 – (±)-*t*-Butyl (2-(3-benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)ethyl)(tosyl)carbamate



16b **34**

Triphenylphosphine (1.53 g, 5.8 mmol) and *t*-butyltosylcarbamate (1.05 g, 3.9 mmol) were dissolved in THF and cooled to 0 °C. DIAD (1.10 mL, 5.8 mmol) was added dropwise followed by addition of **16b** (1.00 g, 3.9 mmol). The mixture was stirred at 0 °C for 30 min before warming to room temperature. After 24 h, the solvent was removed under reduced pressure to give a brown oil. Excess diethyl ether was added forming a white precipitate which was removed by filtration. The solvent was removed from the filtrate under reduced pressure to give a colourless oil which was purified by column chromatography (10% ethyl acetate/petroleum ether) giving the pure product **34** (0.96 g, 48%) as a colourless solid; **m.p.** (diethyl ether) 153-155 °C; **IR** υ_{max}/cm^{-1} 2980, 1725, 1702, 1167, 1156; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H, C*H* arom.), 7.36 – 7.20 (m, 7H, C*H* arom.), 6.18 (d, *J* 0.9, 1H, *H*-7), 4.62 (d, *J* 15.1, 1H, PhC*H*$_2$), 4.58 (d, *J* 15.1, 1H, PhC*H*$_2$), 4.00 (ddd, *J* 14.5, 8.2, 7.0, 1H, *H*-1'), 3.88 (ddd, *J* 14.5, 8.2, 5.5, 1H, *H*-1'), 3.80 (d, *J* 3.0, 1H, *H*-5), 3.62 (m, 1H, *H*-1), 2.72 – 2.52 (m, 2H, *H*-2'), 2.43 (s, 3H, Ar-C*H*$_3$), 1.31 (s, 9H, -C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.0 (*C*=O), 174.3 (*C*=O), 150.0 (*C*=O), 144.4 (*C* arom.), 137.3 (*C* arom.), 136.0 (*C* arom.), 132.3 (*C*-7), 129.4 (*C*H arom.), 128.7 (*C*H arom.), 128.5 (*C*H arom.), 127.9 (*C*H arom.), 127.9 (*C*H arom.), 84.7 (-O*C*(CH$_3$)$_3$), 48.8 (*C*-5), 44.4 (*C*-1), 44.0 (*C*-1'), 42.2 (Ph*C*H$_2$), 30.9 (*C*-2'), 27.9 (-OC(*C*H$_3$)$_3$), 21.7 (Ar-*C*H$_3$); **HRMS** (ESI$^+$) 533.1714 $[M + Na]^+$ ($C_{27}H_{30}N_2NaO_6S$ requires 533.1717).

40 – (±)-2-(3-Azabicyclo[3.2.0]hept-6-en-6-yl)ethan-1-ol

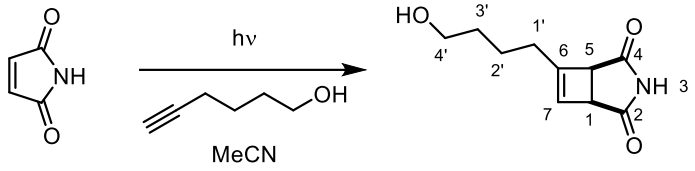


16a **40**

16a (1.00 g 5.98 mmol,) was dissolved in dry THF and cooled to 0 °C. A solution of lithium aluminium hydride (2.40 M in THF, 6.00 mL) was added dropwise forming a white precipitate. After addition was complete the reaction mixture was heated to 60 °C and left for 18 h. The reaction was quenched with addition of water (1.0 mL) and aqueous sodium hydroxide solution (2.0 M, 0.5 mL), stirred for 10 min and then filtered, washed with THF and the filtrate dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give the

pure product **40** (0.61 g, 73%) as a yellow oil; **IR** υ_{max}/cm^{-1} 3280, 2928, 2863, 1631, 1527, 1416; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.67 (s, 1H, *H*-7), 3.68 (td, *J* 6.4, 1.0, 2H, *H*-1'), 3.15 – 3.09 (m, 3H, *H*-5 & N*H*/O*H*), 3.05 (m, 1H, *H*-1), 2.80 (d, *J* 11.9, 1H, *H*-4), 2.69 (d, *J* 11.9, 1H, *H*-2), 2.29 (dd, *J* 11.9, 1.8, 1H, *H*-2), 2.27 (dd, *J* 11.9, 1.9, 1H, *H*-4), 2.22 – 2.16 (m, 2H, *H*-2'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.5 (*C*-6), 129.9 (*C*-7), 59.8 (*C*-1'), 48.5 (*C*-5), 46.6 (*C*-2), 45.7 (*C*-4), 44.3 (*C*-1), 32.8 (*C*-2'); **HRMS** (ESI^+) 152.1076 $[M + H]^+$, ($C_9H_{14}NO$ requires 152.1070).

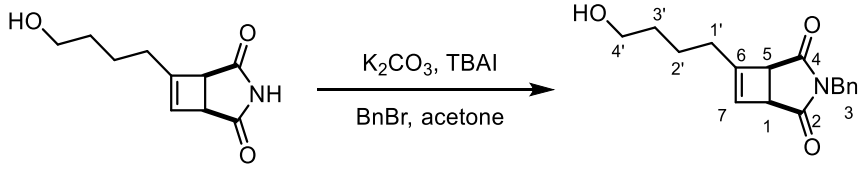
S1 – (±)-6-(4-Hydroxybutyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione



S1

Maleimide (1.46 g, 15 mmol) and 5-hexyn-1-ol (2.5 mL, 22.5 mmol) were dissolved in degassed acetonitrile (150 mL) and irradiated with a 125 W UV lamp. After 16 h, the solvent was removed under reduced pressure and the crude product purified by column chromatography (50% ethyl acetate/petroleum ether) to give the pure product **S1** (1.67 g, 39%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3343, 3234, 2937, 1762, 1703; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (s, 1H, N*H*), 6.11 (m, 1H, *H*-7), 3.71 (m, 1H, *H*-5), 3.68 – 3.58 (m, 3H, *H*-4' & *H*-1), 2.26 – 2.18 (m, 2H, *H*-1'), 1.63 – 1.51 (m, 4H, H-2' & *H*-3'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6 (C=O), 174.9 (C=O), 153.5 (*C*-6), 129.5 (*C*-7), 62.3 (*C*-4'), 50.0 (*C*-5), 45.3 (*C*-1), 32.0 (*C*-2'), 29.7 (*C*-1'), 22.2 (*C*-3'); **HRMS** (ESI^+) 196.0694 $[M + H]^+$ 218.0796 $[M + Na]^+$ ($C_{10}H_{14}NO_3$ requires 196.0968, $C_{10}H_{13}NNaO_3$ requires 218.0788).

43 – (±)-3-Benzyl-6-(4-hydroxybutyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione

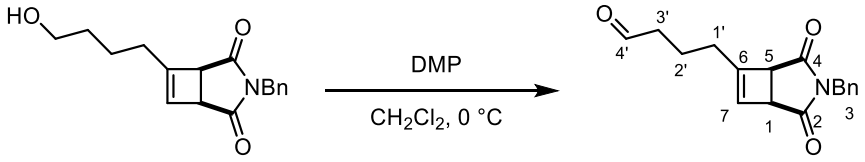


S1 **43**

S1 (1.67 g, 8.55 mmol), benzyl bromide (1.12 mL, 9.41 mmol), potassium carbonate (1.77 g, 12.8 mmol) and tetrabutylammonium iodide (0.16 g, 0.43 mmol) were dissolved in acetone (20 mL) and the resulting suspension heated at reflux for 18 h. After cooling to room temperature, the solids were removed by filtration and the solvent removed from the filtrate under reduced pressure to give the crude product. The crude product was purified by column chromatography (50% ethyl acteate/petroleum ether) to give the pure product **43** as a pale yellow oil (1.55 g, 64%); **IR** υ_{max}/cm^{-1} 3447 (br), 2937, 1764, 1698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.14 (m, 5H, C*H* arom.) 6.08 (m, 1H, *H*-7), 4.62 (d, *J* 14.2, 1H, PhCH_2), 4.57 (d, *J* 14.2, 1H, PhCH_2),

3.68 (m, 1H, *H*-1/5), 3.61 (m, 1H, *H*-1/5), 3.56 (t, *J* 6.0, 2H, *H*-4'), 2.21 – 2.14 (m, 2H, *H*-1'), 1.57 – 1.41 (m, 4H, *H*-2' & *H*-3'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.3 (C=O), 174.5 (C=O), 153.7 (*C*-6), 135.9 (*C* arom.), 129.7 (*C*-7), 129.7 (*C*H arom.), 128.6 (*C*H arom.), 128.47 (*C*H arom.), 127.8 (*C*H arom.), 62.3 (*C*-4'), 48.6 (*C*-1/5), 43.9 (*C*-1/5), 42.0 (Ph*C*H_2), 32.0 (*C*-3'), 29.6 (*C*-1'), 22.3 (*C*-2'); **HRMS** (ESI$^+$) 286.1448 $[M + H]^+$ ($C_{17}H_{20}NO_3$ requires 286.1438).

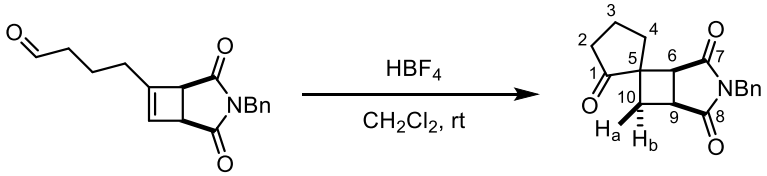
44 – (±)-4-(3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)butanal



43 **44**

43 (1.56 g, 5.43 mmol) was dissolved in DCM (20 mL) and cooled to 0 °C. Dess-Martin periodinane (2.77 g, 6.52 mmol) was added dropwise and after 1 h the solution warmed to room temperature. After a further 3 h of stirring at room temperature, the reaction was quenched by the addition of sodium hydrogen carbonate solution (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give the crude product. Column chromatography (50% ethyl acetate/petroleum ether) was used to afford the pure product **44** as a colourless oil (0.61 g, 40%); **IR** υ_{max}/cm^{-1} 2935 (*C*-H), 1765 (C=O), 1694 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.65 (s, 1H, *H*-4'), 7.37 – 7.21 (m, 5H, C*H* arom.), 6.10 (s, 1H, *H*-7), 4.62 (d, *J* 14.2, 1H, $PhCH_2$), 4.57 (d, *J* 14.2, 1H, $PhCH_2$), 3.68 (d, *J* 3.1, 1H, *H*-5), 3.62 (m, 1H, *H*-1), 2.32 (t, *J* 7.3, 2H, *H*-3'), 2.17 (t, *J* 7.3, 2H, *H*-1'), 1.75 (*app.* p, *J* 7.3, 2H, *H*-2'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.4 (*C*-4'), 175.1 (*C*-2/4), 174.3 (*C*-2/4), 152.8 (*C*-6), 135.8 (*C*-7), 130.4 (*C* arom.), 128.6 (*C*H arom.), 128.5 (*C*H arom.), 127.8 (*C*H arom.), 48.6 (*C*-5), 43.9 (*C*-1), 42.8 (*C*-3'), 42.0 (Ph*C*H_2), 29.2 (*C*-1'), 18.4 (*C*-2'); **HRMS** (ESI$^+$) 284.1279 $[M + H]^+$, 306.1107 $[M + Na]^+$ ($C_{17}H_{18}NO_3$ requires 284.1281, $C_{17}H_{17}NNaO_3$ requires 306.1101).

46 – (±)-3-Benzyl-3-azaspiro[bicyclo[3.2.0]heptane-6,1'-cyclopentane]-2,2',4-trione



44 **46**

Aldehyde **44** (0.12 g, 0.42 mmol) was dissolved in DCM (3.0 mL) and stirred at room temperature. Tetrafluoroboric acid (0.086 mL, 0.63 mmol) was added dropwise causing the solution to turn bright yellow. After 20 min the reaction was quenched by addition of saturated sodium hydrogen carbonate solution (3 mL). The aqueous layer was extracted with DCM (3 ×

5 mL), and the combined organic extracts dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give the crude product. Column chromatography (40% ethyl acetate/petroleum ether) afforded the pure product **46** (13.5 mg, 11%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2924, 2852, 1738, 1702; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.19 (m, 5H, C*H* arom.), 4.69 (s, 2H, PhCH_2), 3.33 (d, *J* 6.7, 1H, *H*-6), 3.22 (ddd, *J* 10.4, 6.7, 4.6, 1H, *H*-9), 2.72 (ddd, *J* 12.8, 10.4, 1.0, 1H, H_b-10), 2.26 (t, *J* 7.4, 2H, *H*-2), 1.95 (m, 1H, *H*-4), 1.86 (dd, *J* 12.8, 4.6, 1H, H_a-10), 1.71 (m, 1H, *H*-3), 1.55 (m, 1H, *H*-3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 218.2 (*C*-1), 178.7 (*C*-8), 176.0 (*C*-7), 135.8 (*C* arom.), 128.9 (*C*H arom.), 128.7 (*C*H arom.), 128.1 (*C*H arom.), 49.8 (*C*-5), 43.2 (*C*-6), 42.6 (Ph*C*H_2), 36.0 (*C*-2), 33.5 (*C*-9), 32.9 (*C*-4), 32.1 (*C*-10), 18.6 (*C*-3); **HRMS** (ESI^+) 306.1109 $[M + Na]^+$ ($C_{17}H_{17}NNaO_3$ requires 306.1101).

4.2.1. General Procedures for Prins Cyclisations

For the products formed from these reactions, IUPAC rules have been used for naming, however a simplified numbering system has been used to facilitate NMR-assignment:

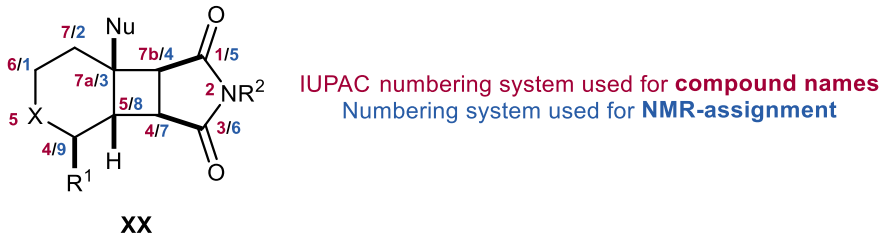


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Figure 21 – Numbering systems used for characterisation of products from the Prins cyclisations of cyclobutenes

4.2.1.1. Prins–Ritter general procedure (A):

Homoallylic alcohol (0.5 mmol) and aldehyde (0.6 mmol) were dissolved in solvent (5 mL) and trifluoromethanesulfonic acid (1 mmol) added dropwise at room temperature. After 20-30 min, the reaction was quenched with sodium hydrogen carbonate (4 mL) before extracting with DCM (3 × 5 mL). The combined organic layers were dried with magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield the crude product which was purified by column chromatography.

4.2.1.2. Prins-Fluoride general procedure (B):

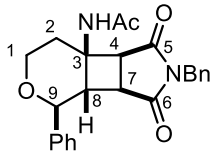
To a solution of homoallylic alcohol (0.58 mmol) and aldehyde (0.70 mmol) in DCM (5 mL) was added trifluoromethanesulfonic acid (0.88 mmol) dropwise. The resulting solution was stirred until completion by TLC. The reaction mixture was quenched with saturated sodium hydrogen carbonate solution (5 mL), extracted with DCM (3 × 5 mL), and the combined organic extracts dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude products were purified by column chromatography.

4.2.1.3. Aza-Prins–Ritter general procedure (C):

34 (0.29 mmol) was dissolved in acetonitrile forming a suspension. Trifluoromethanesulfonic acid (0.44 mmol) was added dropwise and the suspension stirred vigorously. After *ca.* 5 min, **34** had dissolved completely, giving a colourless solution, and TLC confirmed an increase in polarity associated with Boc-deprotection. Aldehyde (0.35 mmol) was then added dropwise forming a yellow solution. Once complete, the reaction was quenched with sat. sodium hydrogen carbonate (2 mL). The product was extracted with DCM (3 × 10 mL) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give the crude product.

4.2.2. Prins–Ritter Reactions

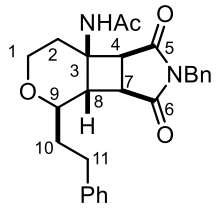
22b – (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-benzyl-1,3-dioxo-4-phenyloctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide



22b

Prepared according to the general procedure A using **16b** and benzaldehyde (1.2 equiv.) and acetonitrile solvent at room temperature and 20 min reaction time. Purified by column chromatography (75% ethyl acetate/petroleum ether) to give the product **22b** (0.10 g, 48%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3298, 1770, 1698, 1659; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.17 (m, 10H, C*H* arom.), 5.56 (s, 1H, N-*H*), 4.79 (d, *J* 6.9, 1H, *H*-9), 4.64 (s, 2H, N-C*H*$_2$), 4.06 – 3.90 (m, 2H, *H*-1), 3.37 (d, *J* 6.6, 1H, *H*-4), 3.27 (dd, *J* 6.9, 5.3, 1H, *H*-8), 3.18 (dd, *J* 6.6, 5.3, 1H, *H*-7), 2.46 (dt, *J* 14.6, 4.6, 1H, *H*-2), 2.11 (ddd, *J* 14.6, 9.9, 6.7, 1H, *H*-2), 1.82 (s, 3H, *H*-11);**^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (*C*-6), 174.4 (*C*-5), 170.7 (*C*-10), 140.2 (*C* arom.), 136.0 (*C* arom.), 128.9 (*C*H arom.), 128.6 (*C*H arom.), 127.9 (*C*H arom.), 127.8 (*C*H arom.), 125.7 (*C*H arom.), 74.7 (*C*-9), 60.9 (*C*-1), 52.8 (*C*-3), 48.8 (*C*-4), 47.3 (*C*-8), 42.9 (-N-*C*H$_2$), 38.7 (*C*-7), 30.7 (*C*-2), 23.5 (*C*-11); **HRMS** (ESI^+) 405.1812 $[M + H]^+$ 427.1631 $[M + Na]^+$ ($C_{24}H_{25}N_2O_4$ requires 405.1809, $C_{24}H_{24}N_2NaO_4$ requires 427.1628).

22a - (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-benzyl-1,3-dioxo-4-phenethyloctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide

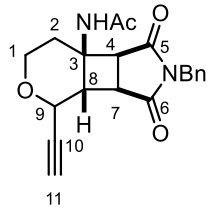


22a

Prepared according to the general procedure A using **16b** and hydrocinnamaldehyde (1.2 equiv.) and acetonitrile solvent at room temperature and 20 min reaction time. Purified by column chromatography (70-90% ethyl acetate/petroleum ether) to give the product **22a** (0.16 g, 75%) as a white solid; **m.p**. 159-160 °C (from methanol); **IR** υ_{max}/cm^{-1} 3299, 1770, 1699, 1660; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.12 (m, 10H, C*H* arom.), 5.74 (s, 1H, N-*H*), 4.63 (s, 2H, PhC*H*$_2$), 3.90 – 3.77 (m, 2H, *H*-1), 3.60 (ddd, *J* 8.5, 6.7, 4.9, 1H, *H*-9), 3.30 (dd, *J* 6.5, 0.9, 1H, *H*-4), 2.89 (dd, *J* 6.5, 5.3, 1H, *H*-7), 2.81 – 2.63 (m, 2H, *H*-11), 2.61 (dd, *J* 6.7, 5.3, 1H, *H*-8), 2.45 (dt, *J* 14.6, 4.0, 1H, *H*-2), 2.01 – 1.82 (m, 2H, *H*-2, *H*-10), 1.80 (s, 3H, C*H*$_3$), 1.79 – 1.72

(m, 1H, *H*-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.5 (*C*-6), 174.6 (*C*-5), 170.6 (*C*-13), 141.4 (*C* arom.), 136.0 (*C* arom.), 128.8 (*C*H arom.), 128.6 (*C*H arom.), 128.5 (*C*H arom.), 128.4 (*C*H arom.), 128.0 (*C*H arom.), 126.0 (*C*H arom.), 72.7 (*C*-9), 60.1 (*C*-1), 52.3 (*C*-3), 48.7 (*C*-4), 47.6 (*C*-8), 42.7 (Ph*C*H_2), 38.5 (*C*-7), 35.9 (*C*-10), 31.4 (*C*-11), 30.4 (*C*-2), 23.5 (*C*H_3); **HRMS** (ESI$^+$) 433.2122 $[M + H]^+$ 455.1941 $[M + Na]^+$ ($C_{26}H_{29}N_2O_4$ requires 433.2122, $C_{26}H_{28}N_2NaO_4$ requires 455.1947).

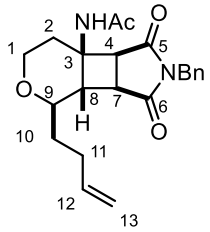
22c - (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-Benzyl-4-ethynyl-1,3-dioxooctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide



22c

Prepared according to general procedure A using **16b** and 3,3-diethoxy-1-propyne (1.2 equiv.) and acetonitrile solvent at room temperature and 21 h reaction time. After the first 2 h, a further portion of triflic acid (3 equiv.) was added. Product purified by column chromatography (40-60% ethyl acetate/petroleum ether) to give the required product **22c** (73 mg, 36%, d.r. 5:1) as a yellow oil; **IR** υ_{max}/cm^{-1} 3273, 2926, 2852, 2125, 1771, 1699, 1661; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.21 (m, 5H, C*H* arom.), 6.20 (s, 1H, N*H*), 4.91 (dd, *J* 3.4, 2.2, 1H, *H*-9), 4.73 (d, *J* 14.0, 1H, PhCH_2), 4.64 (d, *J* 14.0, 1H, PhCH_2), 3.93 (dd, *J* 7.7, 4.7, 2H, *H*-1), 3.48 (t, *J* 6.5, 1H, *H*-7), 3.15 (dd, *J* 6.5, 1.0, 1H, *H*-4), 2.71 (dd, *J* 6.5, 3.4, 1H, *H*-8), 2.60 (d, *J* 2.2, 1H, *H*-11), 2.25 (dt, *J* 15.0, 4.7, 1H, *H*-2), 1.94 (dt, *J* 15.0, 7.7, 1H, *H*-2), 1.79 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (*C*-6), 175.6 (*C*-6), 169.6 (C=O), 135.5 (*C* arom.), 128.7 (*C*H arom.), 128.6 (*C*H arom.), 128.1 (*C*H arom.), 79.3 (*C*-10), 75.3 (*C*-11), 64.8 (*C*-9), 63.5 (*C*-1), 51.0 (*C*-3), 46.7 (*C*-8), 46.5 (*C*-4), 42.8 (Ph*C*H_2), 35.9 (*C*-7), 35.5 (*C*-2), 23.2 (*C*H_3); **HRMS** (ESI$^+$) 375.1329 $[M + Na]^+$ ($C_{20}H_{20}N_2NaO_4$ requires 375.1315).

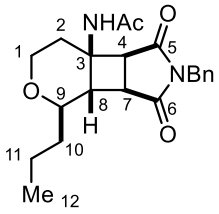
22d - (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-Benzyl-4-(but-3-en-1-yl)-1,3-dioxooctahydropyrano[3',4':3,4]cyclo-buta[1,2-c]pyrrol-7a(1H)-yl)acetamide



22d

Following general procedure A, the reaction was conducted with **16b** and 4-pentenal (1.2 equiv.). The product was purified by column chromatography (75% ethyl acetate/petroleum ether) to give **22d** (94.4 mg, 42%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3298, 2973, 2927, 2873, 1769, 1700, 1665; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.20 (m, 5H, C*H* arom.), 5.77 (ddt, *J* 16.9, 10.2, 6.6, 1H, *H*-12), 5.56 (s, 1H, N*H*), 5.11 – 4.90 (m, 2H, *H*-13), 4.64 (s, 2H, PhCH_2), 3.84 (dd, *J* 8.8, 4.1, 2H, *H*-1), 3.62 (m, 1H, *H*-9), 3.32 (d, *J* 6.5, 1H, *H*-4), 2.95 (t, *J* 6.5, 1H, *H*-7), 2.58 (t, *J* 6.5, 1H, *H*-8), 2.47 (dt, *J* 14.6, 4.1, 1H, *H*-2), 2.24 – 2.08 (m, 2H, *H*-11), 2.02 (m, 1H, *H*-2), 1.81 (s, 3H, CH_3), 1.72 – 1.46 (m, 2H, *H*-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.4 (*C*-6), 174.6 (*C*-5), 170.4 (C=O), 137.7 (*C*-12), 136.0 (*C* arom.), 128.8 (*C*H arom.), 128.6 (*C*H arom.), 128.0 (*C*H arom.), 115.3 (*C*-13), 73.1 (*C*-9), 60.2 (*C*-1), 52.4 (*C*-3), 48.6 (*C*-4), 47.7 (*C*-8), 42.7 (Ph*C*H_2), 38.5 (*C*-7), 33.6 (*C*-10), 30.4 (*C*-2), 29.4 (*C*-11), 23.5 (*C*H_3); **HRMS** (ESI^+) 405.1786 $[M + Na]^+$ ($C_{22}H_{26}N_2NaO_4$ requires 405.1785).

22e - (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-benzyl-1,3-dioxo-4-propyloctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide

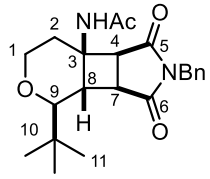


22e

Prepared according to the general procedure A using **16b** and butryaldehyde (1.2 equiv.) and acetonitrile solvent at room temperature and 30 min reaction time. Product purified by column chromatography (50% ethyl acetate/petroleum ether) to give the required product **22e** as a colourless oil (129 mg, 60%); **IR** υ_{max}/cm^{-1} 3300, 2957, 2871, 1768, 1701, 1662; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H, C*H* arom.), 7.34 – 7.25 (m, 3H, C*H* arom.), 5.59 (s, 1H, N*H*), 4.67 (s, 2H, PhCH_2), 3.86 (dd, *J* 8.8, 4.0, 2H, *H*-1), 3.64 (m, 1H, *H*-9), 3.35 (dd, *J* 6.5, 1.0, 1H, *H*-4), 2.97 (dd, *J* 6.5, 5.2, 1H, *H*-7), 2.58 (m, 1H, *H*-8), 2.51 (dtd, *J* 14.7, 4.2, 1.0, 1H, *H*-2), 2.05 (m, 1H, *H*-2), 1.84 (s, 3H, CH_3), 1.67 – 1.29 (m, 4H, *H*-10 & *H*-11), 0.94 (t, *J*

7.0, 3H, *H*-12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.5 (*C*-6), 174.6 (*C*-5), 170.5 (C=O), 136.0 (*C* arom.), 128.9 (*C*H arom.), 128.6 (*C*H arom.), 128.0 (*C*H arom.), 73.7 (*C*-9), 60.3 (*C*-1), 52.5 (*C*-3), 48.7 (*C*-4), 47.9 (*C*-8), 42.8 (Ph*C*H_2), 38.7 (*C*-7), 36.6 (*C*-10/11), 30.3 (*C*-2), 23.5 (*C*H_3), 18.7 (*C*-10/11), 14.0 (*C*-12); **HRMS** (ESI^+) 393.1800 $[M + Na]^+$ ($C_{21}H_{26}N_2NaO_4$ requires 393.1785).

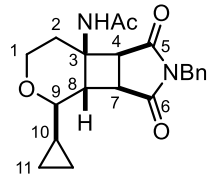
22f - (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-Benzyl-4-(*tert*-butyl)-1,3-dioxooctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide



22f

Prepared according to the general procedure A using **16b** and trimethylacetaldehyde (1.2 equiv.) acetonitrile solvent at room temperature and 30 min reaction time. Product purified by column chromatography (50-80% ethyl acetate/petroleum ether) to give the required product **22f** (102 mg, 46%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3290, 2955, 1769, 1698, 1660; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.34 (m, 2H, C*H* arom.), 7.34 – 7.21 (m, 3H, C*H* arom.), 5.32 (s, 1H, N*H*), 4.68 (d, *J* 13.9, 1H, PhCH_2), 4.64 (d, *J* 13.9, 1H, PhCH_2), 3.98 – 3.77 (m, 2H, *H*-1), 3.35 (d, *J* 6.5, 1H, *H*-4), 3.19 (d, *J* 9.2, 1H, *H*-9), 2.89 (dd, *J* 6.5, 5.1, 1H, *H*-7), 2.72 (dd, *J* 9.2, 5.1, 1H, *H*-8), 2.53 (m, 1H, *H*-2), 2.01 (ddd, *J* 14.5, 10.6, 8.2, 1H, *H*-2), 1.84 (s, 3H, CH_3), 0.90 (s, 9H, *H*-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (*C*-6), 174.2 (*C*-5), 170.5 (C=O), 136.2 (*C* arom.), 128.9 (*C*H arom.), 128.6 (*C*H arom.), 128.0 (*C*H arom.), 81.8 (*C*-9), 62.2 (*C*-1), 53.3 (*C*-3), 48.9 (*C*-4), 44.4 (*C*-8), 42.8 (Ph*C*H_2), 39.6 (*C*-7), 34.1 (*C*-10), 28.8 (*C*-2), 25.6 (*C*-11), 23.6 (*C*H_3); **HRMS** (ESI^+) 385.2127 $[M + H]^+$ 408.1983 $[M + Na]^+$ ($C_{22}H_{29}N_2O_4$ requires 385.2122, $C_{22}H_{29}N_2NaO_4$ requires 408.2020).

22g - (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-Benzyl-4-cyclopropyl-1,3-dioxooctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide

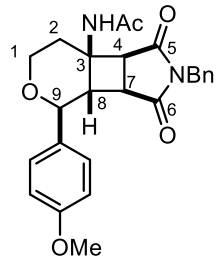


22g

Prepared according to the general procedure A using **16b** and cyclopropanecarboxaldehyde (1.2 equiv.) acetonitrile solvent at room temperature and 50 min reaction time. Product purified by column chromatography (20-50% ethyl acetate/petroleum ether) to give the required

product **22g** (92 mg, 43%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3288, 2877, 1769, 1700, 1663; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H, C*H* arom.), 7.32 – 7.23 (m, 3H, C*H* arom.), 5.67 (s, 1H, N*H*), 4.67 (d, *J* 14.1, 1H, PhC*H*$_2$), 4.63 (d, *J* 14.1, 1H, PhC*H*$_2$), 3.95 (td, *J* 11.0, 5.0, 1H, *H*-1), 3.84 (ddd, *J* 11.0, 6.4, 3.6, 1H, *H*-1), 3.30 (d, *J* 6.5, 1H, *H*-4), 3.04 – 2.88 (m, 2H, *H*-7 & *H*-9), 2.78 (t, *J* 5.5, 1H, *H*-8), 2.47 (ddd, *J* 14.7, 5.0, 3.6, 1H, *H*-2), 1.98 (m, 1H, *H*-2), 1.82 (s, 3H, C*H*$_3$), 1.06 (qt, *J* 8.3, 4.9, 1H, *H*-10), 0.61 – 0.49 (m, 2H, *H*-11), 0.36 (m, 1H, *H*-11), 0.25 (m, 1H, *H*-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.4 (*C*-6), 174.8 (*C*-5), 170.2 (*C*=O), 135.9 (*C* arom.), 128.9 (*C*H arom.), 128.6 (*C*H arom.), 128.0 (*C*H arom.), 78.9 (*C*-9), 60.1 (*C*-1), 52.3 (*C*-3), 48.4 (*C*-4), 47.1 (*C*-8), 42.8 (Ph*C*H$_2$), 39.0 (*C*-7), 31.3 (*C*-2), 23.6 (CH_3), 14.3 (*C*-10), 3.1 (*C*-11), 2.2 (*C*-11); **HRMS** (ESI$^+$) 369.1811 $[M + H]^+$ 391.1637 $[M + Na]^+$ ($C_{21}H_{25}N_2O_4$ requires 369.1809, $C_{21}H_{24}N_2NaO_4$ requires 391.1628).

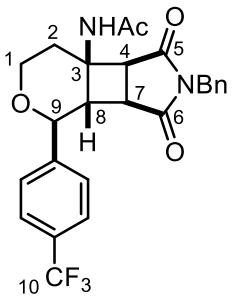
22h - (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-Benzyl-4-(4-methoxyphenyl)-1,3-dioxooctahydropyrano[3',4':3,4]cyclo-buta[1,2-c]pyrrol-7a(1H)-yl)acetamide



22h

Prepared according to the general procedure A using **16b** and *para*-methoxybenzaldehyde (1.2 equiv.) and acetonitrile solvent at room temperature and 30 min reaction time. Purified by column chromatography (60% ethyl acetate/petroleum ether) to give the product **22h** (0.11 g, 51%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3299, 1772, 1698, 1659; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 7H, C*H* arom.), 6.94 – 6.89 (m, 2H, C*H* arom.), 6.14 (s, 1H, N*H*), 5.26 (d, *J* 2.9, 1H, *H*-9), 4.67 (d, *J* 14.1, 1H, PhC*H*$_2$), 4.58 (d, *J* 14.1, 1H, PhC*H*$_2$), 4.18 – 4.06 (m, 2H, *H*-1), 3.81 (s, 3H, -OC*H*$_3$), 3.28 (t, *J* 6.0, 1H, *H*-4), 3.20 (dd, *J* 6.0, 0.9, 1H, *H*-7), 2.93 (ddd, *J* 6.0, 2.9, 0.9, 1H, *H*-8), 2.52 (dt, *J* 14.6, 5.9, 1H, *H*-2), 1.92 (ddd, *J* 14.6, 6.9, 5.9, 1H, *H*-2), 1.84 (s, 3H, *H*-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.4 (*C*-6), 175.9 (*C*-5), 169.6 (*C*-10), 159.3 (C arom.), 135.6 (*C* arom.), 130.9 (*C*H arom.), 128.7 (*C*H arom.), 128.6 (*C*H arom.), 128.1 (*C*H arom.) 127.0 (*C*H arom.), 113.8 (*C*H arom.), 73.9 (*C*-9), 63.3 (*C*-1), 55.2 (-O*C*H$_3$), 52.4 (*C*-3), 48.4 (*C*-8), 46.0 (*C*-7), 42.6 (Ph*C*H$_2$), 35.1 (*C*-4), 34.1 (*C*-2), 23.5 (*C*-11); **HRMS** (ESI$^+$) 435.1905 $[M + H]^+$ 457.1727 $[M + Na]^+$ ($C_{25}H_{27}N_2O_5$ requires 435.1914, $C_{25}H_{26}N_2NaO_5$ requires 457.1734).

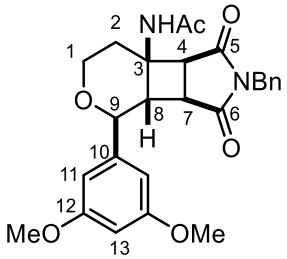
22i - (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-Benzyl-1,3-dioxo-4-(4-(trifluoromethyl)phenyl)octahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide



22i

Prepared according to the general procedure A using **16b** and *para*-trifluoromethylbenzaldehyde (1.2 equiv.) and acetonitrile solvent at room temperature and 21 h reaction time. Purified by column chromatography (40% ethyl acetate/petroleum ether) to give the product **22i** (80 mg, 40%) as a white solid; **m.p.** (methanol) 199-200 °C; **IR** υ_{max}/cm^{-1} 3456, 1771, 1699, 1643; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.63 (d, *J* 8.7, 2H, C*H* arom.), 7.60 (d, *J* 8.7, 2H, C*H* arom.), 7.39 – 7.14 (m, 5H, C*H* arom.), 4.90 (d, *J* 8.4, 1H, *H*-9), 4.61 (d, *J* 14.5, 1H, PhC*H*$_2$), 4.56 (d, *J* 14.5, 1H, PhC*H*$_2$), (ddd, *J* 11.0, 7.0, 2.4, 1H, *H*-1), 4.01 (td, *J* 11.0, 5.4, 1H, *H*-1), 3.47 (d, *J* 6.6, 1H, *H*-4), 3.35 (dd, *J* 6.6, 5.2, 1H, *H*-7), 3.24 (dd, *J* 8.4, 5.2, 1H, *H*-8), 2.48 (ddd, *J* 14.8, 5.4, 2.4, 1H, *H*-2), 2.35 (ddd, *J* 14.8, 11.0, 7.0, 1H, *H*-2), 1.84 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, CD_3OD) δ 178.1 (*C*-6), 175.2 (*C*-5), 172.6 (*C*=O), 145.6 (*C* arom.), 136.1 (*C* arom.), 129.3 (q, *J* 32.4, *C*-10) 128.2 (*C*H arom.), 127.9 (*C*H arom.), 127.3 (*C*H arom.), 126.1 (*C*H arom.), 124.9 (q, *J* 3.82, *C*-CF_3), 73.5 (*C*-9), 61.1 (*C*-1), 52.7 (*C*-3), 49.2 (*C*-4), 47.6 (*C*-8), 42.2 (N-*C*H$_2$), 38.4 (*C*-7), 29.0 (*C*-2), 21.6 (*C*-11); **HRMS** (ESI^+) 473.1686 $[M + H]^+$ 495.1506 $[M + Na]^+$ ($C_{25}H_{24}F_3N_2O_4$ requires 473.1643, $C_{25}H_{23}F_3N_2NaO_4$ requires 495.1502).

22j - (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-Benzyl-4-(3,5-dimethoxyphenyl)-1,3-dioxooctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide

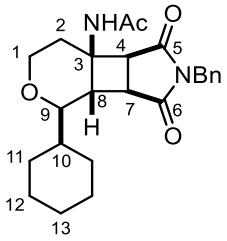


22j

Prepared according to the general procedure A using **16b** and 3,5-dimethoxybenzaldehyde (1.2 equiv.) and acetonitrile solvent at room temperature and 1.5 h reaction time. Product purified by column chromatography (25% ethyl acetate/petroleum ether) to give the required

product **22j** (66 mg, 24%) as an orange solid. **IR** υ_{max}/cm^{-1} 3309, 2938, 1769, 1701, 1664, 1597; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H, C*H* arom.), 7.36 – 7.26 (m, 3H, C*H* arom.), 6.59 (d, *J* 2.5, 2H, *H*-11), 6.40 (t, *J* 2.5, 1H, *H*-13), 5.48 (s, 1H, N-*H*), 4.78 (m, 1H, *H*-9), 4.71 (d, *J* 14.1, 1H, PhCH_2), 4.67 (d, *J* 14.1, 1H, PhCH_2), 4.10 – 3.98 (m, 2H, *H*-1), 3.82 (s, 6H, -OCH_3), 3.44 (m, 1H, *H*-4), 3.31 – 3.26 (m, 2H, *H*-7 and *H*-8), 2.56 (dt, *J* 14.6, 4.6, 1H, *H*-2), 2.15 (m, 1H, *H*-2), 1.88 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.1 (*C*-6), 174.3 (*C*-5), 170.6 (*C*=O), 161.0 (*C*-12), 142.7 (*C*-10), 136.1 (*C* arom.), 128.9 (*C*H arom.), 128.6 (*C*H arom.), 127.9 (*C*H arom.), 103.4 (*C*-11), 100.1 (*C*-13), 74.4 (*C*-9), 60.9 (*C*-1), 55.5 (-O*C*H_3), 52.7 (*C*-3), 48.8 (*C*-4), 47.6 (*C*-8), 42.9 (Ph*C*H_2), 38.8 (*C*-7), 30.6 (*C*-2), 23.6 (*C*H_3); **HRMS** (ESI^+) 487.1837 $[M + Na]^+$ ($C_{26}H_{28}N_2NaO_6$ requires 487.1840).

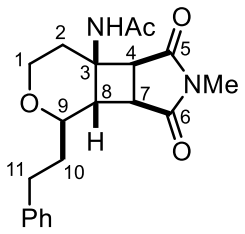
22k – (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-Benzyl-4-cyclohexyl-1,3-dioxooctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide



22k

Prepared according to the general procedure A using **16b** and cyclohexanecarboxaldehyde (1.2 equiv.) and acetonitrile solvent at room temperature and 30 min reaction time. Product purified by column chromatography (50% ethyl acetate/petroleum ether) to give the required product **22k** (105 mg, 44%) as a white solid; **m.p.** 147-149 °C (from ethyl acetate) **IR** υ_{max}/cm^{-1} 3304, 2924, 2853, 1769, 1702, 1658; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H, C*H* arom.), 7.33 – 7.24 (m, 3H, *C*H arom.), 5.39 (s, 1H, N*H*), 4.69 (d, *J* 14.0, 1H, PhCH_2), 4.64 (d, *J* 14.0, 1H, PhCH_2), 3.90 – 3.83 (m, 2H, *H*-1), 3.35 (d, *J* 6.5, 1H, *H*-4), 3.25 (t, *J* 8.0, 1H, *H*-9), 2.92 (dd, *J* 6.5, 5.1, 1H, *H*-7), 2.70 (dd, *J* 8.0, 5.1, 1H, *H*-8), 2.51 (dt, *J* 15.1, 4.0, 1H, *H*-2), 2.01 (m, 1H, *H*-2), 1.82 (s, 3H, CH_3), 1.95 – 1.60 (m, 6H, CH_2), 1.37 (m, 1H, *H*-10), 1.27 – 1.11 (m, 2H, CH_2), 1.03 – 0.81 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (*C*-6), 174.4 (*C*-5), 170.4 (*C*=O), 136.1 (*C* arom.), 128.9 (*C*H arom.), 128.6 (*C*H arom.), 128.0 (*C*H arom.), 78.5 (*C*-9), 61.3 (*C*-1), 52.8 (*C*-3), 48.8 (*C*-4), 46.5 (*C*-8), 42.8 (Ph*C*H_2), 42.6 (*C*-10), 39.1 (*C*-7), 29.6 (*C*-2), 29.4 (*C*H_2), 28.1 (*C*H_2), 26.5 (*C*H_2), 25.9 (*C*H_2), 25.7 (*C*H_2), 23.6 (*C*H_3); **HRMS** (ESI^+) 411.2272 $[M + H]^+$ 433.2102 $[M + Na]^+$ ($C_{24}H_{31}N_2O_4$ requires 411.2278, $C_{24}H_{30}N_2NaO_4$ requires 433.2098).

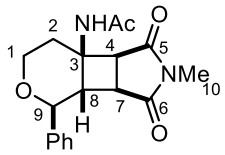
29a – (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-Methyl-1,3-dioxo-4-phenethyloctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide



29a

Prepared according to the general procedure A using **16c** and hydrocinnamaldehyde (1.2 equiv.), acetonitrile solvent at room temperature and 2 h reaction time. Product purified by column chromatography (50-75% ethyl acetate/petroleum ether) to give the required product **29a** (280 mg, 95%) as a white solid; **m.p.** (methanol) 128-130 °C; **IR** υ_{max}/cm^{-1} 2929, 1769, 1696; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 2H, C*H* arom.), 7.16 – 7.09 (m, 3H, C*H* arom.), 5.55 (s, 1H, N*H*), 3.85 – 3.79 (m, 2H, *H*-1), 3.54 (ddd, *J* 8.5, 6.6, 5.1, 1H, *H*-9), 3.20 (d, *J* 6.4, 0.8, 1H, *H*-4), 2.94 (s, 3H, N-CH_3), 2.91 (dd, *J* 6.6, 5.5, 1H, *H*-8), 2.86 (dd, *J* 6.4, 5.5, 1H, *H*-7), 2.76 – 2.56 (m, 2H, *H*-10), 2.27 (dt, *J* 13.5, 3.4, 1H, *H*-2), 1.99 (m, 1H, *H*-2), 1.87 (s, 3H, CH_3), 1.87 – 1.65 (m, 2H, *H*-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.9 (*C*=O), 175.2 (*C*=O), 170.7 (*C*=O), 141.4 (*C* arom.), 128.5 (*C*H arom.), 128.4 (*C*H arom.), 126.0 (*C*H arom.), 72.8 (*C*-9), 59.7 (*C*-1), 52.0 (*C*-3), 49.2 (*C*-4), 46.9 (*C*-8), 38.4 (*C*-7), 35.8 (*C*-11), 31.5 (*C*-2), 31.4 (*C*-10), 25.4 (N-*C*H_3), 23.8 (*C*H_3); **HRMS** (ESI^+) 357.1819 $[M + H]^+$ 379.1645 $[M + Na]^+$ ($C_{20}H_{25}N_2O_4$ requires 357.1809, $C_{20}H_{24}N_2NaO_4$ requires 379.1628).

29b – (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-methyl-1,3-dioxo-4-phenyloctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide

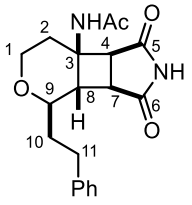


29b

Following general procedure A, the reaction was conducted with **16c** and benzaldehyde dimethyl acetal. The product was purified by column chromatography (70% ethyl acetate/petroleum ether) to give **29b** (0.12 g, 43%) as a yellow solid; **m.p.** (methanol) 186-188 °C ; **IR** υ_{max}/cm^{-1} 3253, 3067, 2849, 1776, 1698, 1554; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.17 (m, 5H, C*H* arom.), 5.56 (s, 1H, N*H*), 4.84 (d, *J* 6.0, 1H, *H*-9), 4.08 – 3.93 (m, 2H, *H*-1), 3.67 (t, *J* 6.0, 1H, *H*-8), 3.37 (d, *J* 7.0, 1H, *H*-4), 3.22 (dd, *J* 7.0, 6.0, 1H, *H*-7), 3.00 (s, 3H, *H*-10), 2.34 (dt, *J* 14.7, 4.5, 1H, *H*-2), 2.15 (ddd, *J* 14.7, 9.8, 6.5, 1H, *H*-2), 1.92 (s, 3H, -CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.7 (*C*-6), 175.2 (*C*-5), 170.9 (*C*=O), 140.3 (*C* arom.), 128.6 (*C*H

arom.), 127.8 (*C*H arom.), 125.7 (*C*H arom.), 74.7 (*C*-9), 60.2 (*C*-1), 52.4 (*C*-3), 49.1 (*C*-4), 46.2 (*C*-8), 38.4 (*C*-7), 31.7 (*C*-2), 25.4 (*C*-10), 23.7 (*C*H$_3$); **HRMS** (ESI$^+$) 329.1504 [M + H]$^+$ 351.1321 [M + Na]$^+$ ($C_{18}H_{21}N_2O_4$ requires 329.1496, $C_{18}H_{20}N_2NaO_4$ requires 351.1315).

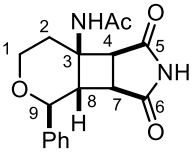
30a – (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-1,3-dioxo-4-phenethyloctahydropyrano[3',4':3,4]cyclobuta-[1,2-c]pyrrol-7a(1H)-yl)acetamide



30a

Following general procedure A, the reaction was conducted with **16a** and hydrocinnamaldehyde. The product was recrystallised from acetonitrile to give **30a** (0.13 g, 42%) as a colourless solid; **m.p.** (acetonitrile) 231 – 232 °C; **IR** υ_{max}/cm^{-1} 3295, 3026, 3943, 3776, 1758, 1706; **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ 11.12 (s, 1H, N*H*), 7.84 (s, 1H, N*H*Ac), 7.36 – 7.06 (m, 5H, C*H* arom.), 3.77 – 3.61 (m, 2H, *H*-1), 3.56 (m, 1H, *H*-9), 3.19 (s, 1H, *H*-4), 2.88 – 2.76 (m, 2H, *H*-7 & *H*-8), 2.70 – 2.55 (m, 2H, *H*-11), 2.42 (m, 1H, *H*-2), 1.99 (ddd, *J* 14.3, 11.7, 6.9, 1H, *H*-2), 1.73 (s, 3H, C*H*$_3$), 1.72 – 1.52 (m, 2H, *H*-10); **^{13}C NMR** (101 MHz, DMSO-d$_6$) δ 180.4 (*C*-6), 176.8 (*C*-5), 170.2 (*C*=O), 142.3 (*C* arom.), 128.7 (*C*H arom.), 126.2 (*C*H arom.), 71.9 (*C*-9), 59.9 (*C*-1), 51.8 (*C*-3), 51.1 (*C*-4), 47.0 (*C*-8), 36.7 (*C*-10), 31.3 (*C*-11), 29.5 (*C*-2), 23.6 (*C*H$_3$); **HRMS** (ESI$^+$) 365.1486 [M + Na]$^+$ ($C_{19}H_{22}N_2NaO_4$ requires 365.1472).

30b – (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-1,3-dioxo-4-phenyloctahydropyrano[3',4':3,4]cyclobuta[1,2-c]-pyrrol-7a(1H)-yl)acetamide

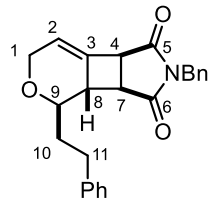


30b

Following general procedure A, the reaction was conducted with **16a** and benzaldehyde. The product was recrystallised from acetonitrile to give **30b** (76.5 mg, 27%) as a colourless solid; **m.p.** (acetonitrile) 261-263 °C; **IR** υ_{max}/cm^{-1} 3237, 1759, 1708; **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ 11.1 (s, 1H, N*H*), 7.94 (s, 1H, N*H*Ac), 7.48 – 7.19 (m, 5H, C*H* arom.), 4.77 (d, *J* 8.6, 1H, *H*-9), 3.96 (m, 1H, *H*-1), 3.86 (ddd, *J* 11.7, 10.3, 5.2, 1H, *H*-1), 3.31 (dd, *J* 6.6, 0.9, 1H, *H*-4), 3.24 (dd, *J* 8.6, 5.2, 1H, *H*-8), 3.16 (dd, *J* 6.6, 5.2, 1H, *H*-7), 2.54 (m, 1H, *H*-2), 2.24 (ddd, *J* 14.4, 11.7, 7.0, 1H, *H*-2), 1.77 (s, 3H, *C*H$_3$); **^{13}C NMR** (101 MHz, DMSO-d$_6$) δ 179.5 (*C*-6), 176.3 (*C*-5), 169.8 (*C*=O), 141.4 (*C* arom.), 128.1 (*C*H arom.), 127.3 (*C*H arom.), 125.9 (*C*H

arom.), 73.4 (*C*-9), 60.9 (*C*-1), 52.1 (*C*-3), 50.7 (*C*-4), 47.5 (*C*-8), 39.6 (*C*-7) 28.5 (*C*-2), 23.2 (*C*H$_3$); **HRMS** (ESI$^+$) 315.1335 [M + H]$^+$ 337.1155 [M + Na]$^+$ ($C_{17}H_{19}N_2O_4$ requires 315.1339, $C_{17}H_{18}FN_2NaO_4$ requires 337.1159).

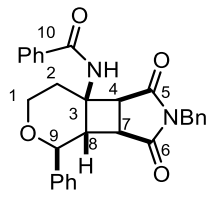
31a – (±)-(3a*S*,3b*S*,4*R*,7b*S*)-2-benzyl-4-phenethyl-3b,4,6,7b-tetrahydropyrano[3',4':3,4]cyclobuta-[1,2-c]pyrrole-1,3(2H,3aH)-dione



31a

Prepared according to the general procedure A using **16b** and hydrocinnamaldehyde (1.2 equiv.) and DCM solvent at room temperature and 24 h reaction time. Purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product **31a** (0.09 g, 50%) as a white solid; **m.p.** (methanol) 123-124 °C; **IR** υ_{max}/cm^{-1} 3027, 1771, 1703; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.19 (m, 10H, C*H* arom.), 5.76 (tt, *J* 3.0, 1.5, 1H, *H*-2), 4.73 (s, 2H, N-C*H*$_2$), 4.44 (dtd, *J* 16.9, 3.0, 1.5, 1H, *H*-1), 4.27 (dtd, *J* 16.9, 3.0, 1.5, 1H, *H*-1), 3.95 (ddt, *J* 5.5, 3.0, 1.5, 1H, *H*-4), 3.24 (dd, *J* 5.5, 4.9, 1H, *H*-7), 3.16 (ddd, *J* 8.6, 7.4, 5.6, 1H, *H*-9), 2.87 – 2.76 (m, 3H, *H*-8 & *H*-11), 1.92 (m, 2H, *H*-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.7 (*C*-6), 174.2 (*C*-5), 141.4 (*C* arom.), 135.7 (*C* arom.), 130.9 (*C*-3), 128.8 (*C*H arom.), 128.7 (*C*H arom.), 128.5 (*C*H arom.), 128.5 (*C*H arom.), 128.0 (*C*H arom.), 126.0 (*C*H arom.), 119.2 (*C*-2), 75.2 (*C*-9), 66.7 (*C*-1), 51.4 (*C*-7), 50.6 (*C*-4), 42.8 (N-*C*H$_2$), 42.7 (*C*-8), 35.3 (*C*-10), 30.9 (*C*-11); **HRMS** (ESI$^+$) 374.1761 [M + H]$^+$ 396.1580 [M + Na]$^+$ ($C_{24}H_{24}NO_3$ requires 374.1751, $C_{24}H_{23}NNaO_3$ requires 396.1570).

57 – (±)-*N*-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-benzyl-1,3-dioxo-4-phenyloctahydropyrano[3',4':3,4]cyclobuta-[1,2-c]pyrrol-7a(1H)-yl)benzamide

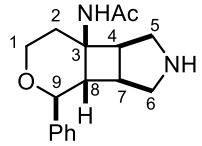


57

Prepared according to the general procedure A using **16b** and benzaldehyde (1.2 equiv.) and benzonitrole solvent at room temperature and 30 min reaction time. Purified by column chromatography (40% ethyl acetate/petroleum ether) to give the product **57** (0.12 g, 53%) as a white solid; **m.p.** (methanol) 195-196 °C; **IR** υ_{max}/cm^{-1} 3347, 1769, 1698, 1663; **^{1}H NMR** (400

MHz, $CDCl_3$) δ 7.61 – 7.13 (m, 15H, C*H* arom.), 6.16 (s, 1H, N*H*), 4.86 (d, *J* 6.5, 1H, *H*-9), 4.65 (s, 2H, CH_2Ph), 4.06 – 3.98 (m, 2H, *H*-1), 3.43 (d, *J* 6.5, 1H, *H*-4), 3.35 (dd, *J* 6.5, 5.3, 1H, *H*-8), 3.26 (dd, *J* 6.5, 5.3, 1H, *H*-7), 2.65 (dt, *J* 14.8, 4.5, 1H, *H*-2), 2.21 (ddd, *J* 14.6, 9.5, 7.2, 1H, *H*-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.1 (*C*-6), 174.4 (*C*-5), 167.9 (*C*-10), 140.1 (*C* arom.), 136.0 (*C* arom.), 134.2 (*C* arom.), 131.7 (*C*H arom.), 128.9 (*C*H arom.), 128.6 (*C*H arom.), 128.6 (*C*H arom.), 128.5 (*C*H arom.), 127.9 (*C*H arom.), 127.9 (*C*H arom.), 127.0 (*C*H arom.), 125.7 (*C*H arom.), 74.7 (*C*-9) 61.0 (*C*-1), 53.0 (*C*-3), 48.8 (*C*-4), 47.6 (*C*-8), 42.9 (*C*H_2Ph), 38.9 (*C*-7), 30.7 (*C*-2); **HRMS** (ESI^+) 467.1947 $[M + H]^+$ 489.1779 $[M + Na]^+$ ($C_{29}H_{27}N_2O_4$ requires 467.1965, $C_{29}H_{26}N_2NaO_4$ requires 489.1785).

41 – (±)-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-4-phenyloctahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrol-7a(1H)-yl)acetamide

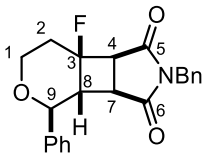


41

Following general procedure A, the reaction was conducted with **40** and benzaldehyde. The product was purified by column chromatography (5% methanol/DCM) to give **41** (161 mg, 78%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3454 (br), 1633, 1538, 1242, 1027; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.38 – 7.24 (m, 5H, C*H* arom.), 4.71 (d, *J* 8.2, 1H, *H*-9), 4.15 (ddd, *J* 10.5, 7.2, 1.9, 1H, *H*-1), 4.05 (ddd, *J* 11.7, 10.5, 5.6, 1H, *H*-1), 3.40 – 3.08 (m, 6H, *H*-5,6,4 & 7), 2.87 (m, 1H, *H*-8), 2.34 (ddd, *J* 14.6, 11.5, 7.3, 1H, *H*-2), 2.21 (ddt, *J* 14.6, 5.6, 1.7, 1H, *H*-2), 2.07 (s, 3H, CH_3); **^{13}C-NMR** (126 MHz, CD_3OD) δ 173.1 (*C*=O), 141.2 (*C* arom.), 128.2 (*C*H arom.), 127.4 (*C*H arom.), 125.7 (*C*H arom.), 75.0 (*C*-9), 61.3 (*C*-1), 51.3 (*C*-3), 50.5 (*C*-5/6), 47.5(*C*-4), 47.2 (*C*-8), 46.8 (*C*-5/6), 37.2 (*C*-7), 29.0 (*C*-2), 21.6 (*C*H_3); **HRMS** (ESI^+) 287.1755 $[M + H]^+$ ($C_{17}H_{23}N_2O_2$ requires 287.1754).

4.2.3. Fluoride Prins Reactions

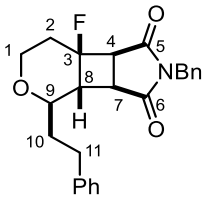
39a - (±)-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-benzyl-7a-fluoro-4-phenylhexahydropyrano[3',4':3,4]cyclobuta-[1,2-c]pyrrole-1,3(2H,3aH)-dione



39a

Following general procedure B, the reaction was conducted with **16b** and benzaldehyde dimethyl acetal. The product was purified by column chromatography (40% ethyl acetate/petroleum ether) to give the pure product **39a** (0.15 g, 71%) as a yellow solid; **m.p.** (ethyl acetate) 137-141 °C; **IR** υ_{max}/cm^{-1} 2964, 2893, 1776, 1699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.15 (m, 10H, C*H* arom.), 4.63 (d, *J* 14.2, 1H, PhC*H*$_2$), 4.58 (d, *J* 14.2, 1H, PhC*H*$_2$), 4.51 (dd, *J* 6.7, 1.9, 1H, *H*-9), 3.98 (dtd, *J* 11.9, 6.0, 1.9, 1H, *H*-1), 3.65 (ddd, *J* 11.9, 7.3, 5.4, 1H, *H*-1), 3.50 (ddd, *J* 8.8, 6.3, 1.2, 1H, *H*-4), 2.96 (ddd, *J* 6.3, 3.7, 2.4, 1H, *H*-7), 2.83 (dddd, *J* 19.1, 6.7, 3.7, 1.2, 1H, *H*-8), 2.16 – 2.02 (m, 2H, *H*-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.6 (*C*-6), 172.4 (d, $^3J_{CF}$ 5.8, *C*-5), 139.3 (*C* arom.), 135.5 (*C* arom.), 128.8 (*C*H arom.), 128.7 (*C*H arom.), 128.4 (*C*H arom.), 128.0 (*C*H arom.), 126.4 (*C*H arom.), 91.6 (d, $^1J_{CF}$ 220.6, *C*-3), 78.8 (d, $^3J_{CF}$ 3.2, *C*-9), 61.3 (d, $^3J_{CF}$ 6.3, *C*-1), 48.2 (d, $^2J_{CF}$ 22.1, *C*-8), 47.9 (d, $^2J_{CF}$ 23.8, *C*-4), 43.0 (*C*H$_2$Ph), 38.3 (d, $^3J_{CF}$ 5.0, *C*-7), 31.7 (d, $^2J_{CF}$ 22.3, *C*-2). **HRMS** (ESI$^+$) 366.1514 $[M + H]^+$ 388.1335 $[M + Na]^+$ ($C_{22}H_{21}FNO_3$ requires 366.1500, $C_{22}H_{20}FNNaO_3$ requires 388.1319).

39b – (±)-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-benzyl-7a-fluoro-4-phenethylhexahydropyrano[3',4':3,4]cyclo-buta[1,2-c]pyrrole-1,3(2H,3aH)-dione

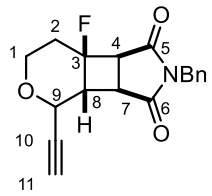


39b

Following general procedure B, the reaction was conducted with **16b** and hydrocinnamaldehyde dimethyl acetal. The product was purified by column chromatography to give **39b** (65.5 mg, 29%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2935, 2860, 1771, 1700, 1495; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.08 (m, 10H, C*H* arom.), 4.73 (d, *J* 14.2, 1H, PhC*H*$_2$), 4.67 (d, *J* 14.2, 1H, PhC*H*$_2$), 4.08 (dtd, *J* 11.7, 6.0, 2.1, 1H, *H*-1), 3.58 (ddd, *J* 11.7, 7.4, 6.0, 1H, *H*-1), 3.46 (ddd, *J* 9.9, 6.4, 1.2, 1H, *H*-4), 3.34 (dddd, *J* 9.8, 7.9, 4.0, 1.7, 1H, *H*-9), 2.85 – 2.65 (m, 3H, *H*-7 & *H*-10), 2.40 (dddd, *J* 19.7, 7.9, 3.2, 1.2, 1H, *H*-8), 2.10 (t, *J* 6.0, 1H, *H*-2), 2.05

(m, 1H, *H*-2), 1.98 (m, 1H, *H*-11), 1.86 (m, 1H, *H*-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.7 (*C*-6), 172.5 (d, *J* 6.5, *C*-5), 141.1 (*C* arom.), 135.5 (*C* arom.), 128.6 (*C*H arom.), 128.5 (*C*H arom.), 128.4 (*C*H arom.), 128.0 (*C*H arom.), 126.1 (*C*H arom.), 92.3 (d, *J* 217.6, *C*-3), 77.1 (d, *J* 3.0, *C*-9), 61.9 (d, *J* 6.9, *C*-1), 47.8 (d, *J* 21.5, *C*-8), 47.6 (d, *J* 23.5, *C*-4), 42.9 (Ph*C*H$_2$), 38.7 (d, *J* 3.5, *C*-7), 36.1 (*C*-11), 31.6 (d, *J* 22.3, *C*-2), 31.2 (*C*-10); **HRMS** (ESI^+) 416.1634 [M + Na]$^+$ ($C_{24}H_{24}FNNaO_3$ requires 416.1632).

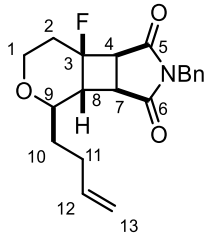
39c – (±)-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-benzyl-4-ethynyl-7a-fluorohexahydropyrano[3',4':3,4]cyclobuta[1,2-c]pyrrole-1,3(2H,3aH)-dione



39c

Following general procedure B, the reaction was conducted with **16b** and 3,3-diethoxy-1-propyne. The product was purified by column chromatography (25% ethyl acetate/petroleum ether) to give the pure product **39c** (56.6 mg, 31%, d.r. 2:1) as a yellow oil; **IR** υ_{max}/cm^{-1} 3270, 2930, 1774, 1698; Major diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 5H, C*H* arom.), 4.73 (s, 2H, PhC*H*$_2$), 4.55 (dd, *J* 4.4, 2.2, 1H, *H*-9), 3.99 (ddd, *J* 12.0, 5.8, 3.9, 1H, *H*-1), 3.62 (ddd, *J* 12.0, 10.5, 3.9, 1H, *H*-1), 3.41 (ddd, *J* 6.3, 3.3, 1.2, 1H, *H*-4), 3.25 (td, *J* 6.3, 3.3, 1H, *H*-7), 2.71 (m, 1H, *H*-8), 2.69 (d, *J* 2.2, 1H, *H*-11), 2.30 (ddtd, *J* 23.1, 15.3, 3.9, 1.2, 1H, *H*-2), 2.12 (m, 1H, *H*-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.6 (*C*-6), 171.9 (d, *J* 3.0, *C*-5), 135.5 (*C* arom.), 128.7 (*C*H arom.), 128.6 (*C*H arom.), 128.1 (*C*H arom.), 87.3 (d, *J* 232.0, *C*-3), 78.3 (d, *J* 1.6, *C*-10), 76.0 (*C*-11), 64.3 (d, *J* 1.8, *C*-9), 62.5 (d, *J* 1.8, *C*-1), 48.8 (d, *J* 22.8, *C*-4), 48.4 (d, *J* 23.1, *C*-8), 42.9 (Ph*C*H$_2$), 33.2 (d, *J* 22.8, *C*-2), 33.1 (d, *J* 11.03, *C*-7); Minor diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 5H, C*H* arom.), 4.75 – 4.67 (m, 3H, *H*-9 & PhC*H*$_2$), 4.17 (m, 1H, *H*-1), 3.83 (dt, *J* 11.9, 5.9, 1H, *H*-1), 3.45 (ddd, *J* 6.2, 4.6, 1.2, 1H, *H*-4), 3.03 (ddd, *J* 6.2, 5.4, 3.3, 1H, *H*-7), 2.78 (m, 1H, *H*-8), 2.58 (d, *J* 2.4, 1H, *H*-11), 2.48 (ddt, *J* 20.6, 15.0, 5.9, 1H, *H*-2), 2.15 (m, 1H, *H*-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.8 (*C*-6), 172.0 (d, *J* 4.1, *C*-5), 135.4 (*C* arom.), 128.7 (*C*H arom.), 128.6 (*C*H arom.), 128.1 (*C*H arom.), 87.7 (d, *J* 230.3, *C*-3), 80.0 (*C*-10), 75.7 (*C*-11), 64.1 (*C*-9), 58.3 (d, *J* 4.2, *C*-1), 49.2 (d, *J* 22.7, *C*-8), 48.6 (d, *J* 23.2, *C*-4), 42.9 (Ph*C*H$_2$), 35.5 (d, *J* 9.5, *C*-7), 32.0 (d, *J* 22.3, *C*-2); **HRMS** (ESI^+) 314.1191 [M + H]$^+$ 336.1014 [M + Na]$^+$ ($C_{18}H_{17}FNO_3$ requires 314.1187, $C_{18}H_{16}FNNaO_3$ requires 336.1006).

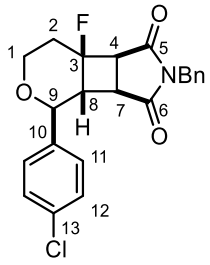
39d – (±)-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-benzyl-4-(but-3-en-1-yl)-7a-fluorohexahydropyrano[3',4':3,4]-cyclobuta[1,2-c]pyrrole-1,3(2H,3aH)-dione



39d

Following general procedure B, the reaction was conducted with **16b** and 4-pentenal. The product was purified by column chromatography to give **39d** (150 mg, 75%) as colourless oil; **IR** υ_{max}/cm^{-1} 2936 (w), 1774 (w), 1704, 1392 (w), 1169; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.22 (m, 5H, C*H* arom.), 5.79 (ddt, *J* 16.9, 10.2, 6.6, 1H, *H*-12), 5.14 – 4.91 (m, 2H, *H*-13), 4.73 (d, *J* 14.2, 1H, PhC*H*$_2$), 4.67 (d, *J* 14.2, 1H, PhC*H*$_2$), 4.05 (dtd, *J* 11.7, 5.7, 2.1, 1H, *H*-1), 3.58 (ddd, *J* 11.7, 8.2, 4.9, 1H, *H*-1), 3.51 (ddd, *J* 10.0, 6.5, 1.2, 1H, *H*-4), 3.41 (tdd, *J* 7.7, 5.0, 1.8, 1H, *H*-9), 2.80 (ddd, *J* 6.5, 3.3, 2.2, 1H, *H*-7), 2.38 (dddd, *J* 19.8, 7.7, 3.3, 1.2, 1H, *H*-8), 2.25 – 2.05 (m, 4H, *H*-2 & *H*-11), 1.84 – 1.55 (m, 2H, *H*-10); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.7 (*C*-6), 172.5 (d, *J* 6.4, *C*-5), 137.5 (*C*-12), 135.5 (*C* arom.), 128.6 (*C*H arom.), 128.0 (*C*H arom.), 115.5 (*C*-13), 92.4 (d, *J* 217.6, *C*-3), 77.5 (d, *J* 3.4, *C*-9), 61.9 (d, *J* 6.9, *C*-1), 47.9 (d, *J* 21.7, *C*-8), 47.6 (d, *J* 24.0, *C*-4), 43.0 (Ph*C*H$_2$), 38.7 (d, *J* 3.5, *C*-7), 33.9 (*C*-10), 31.6 (d, *J* 22.3, *C*-2), 29.3 (*C*-11); **HRMS** (ESI^+) 366.1476 $[M + Na]^+$ ($C_{20}H_{22}FNNaO_3$ requires 366.1476).

39e – (±)-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-benzyl-4-(4-chlorophenyl)-7a-fluorohexahydropyrano[3',4':3,4]-cyclobuta[1,2-c]pyrrole-1,3(2H,3aH)-dione

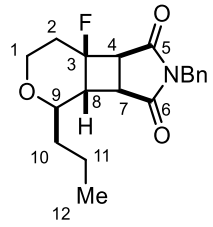


39e

Following general procedure B, the reaction was conducted with **16b** and *para*-chlorobenzaldehyde dimethyl acetal. The product was purified by recrystallisation from methanol to give **39e** (85 mg, 37%) as colourless crystals; **m.p.** (methanol) 125-126 °C; **IR** υ_{max}/cm^{-1} 1767, 1696, 1493; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.20 (m, 9H, C*H* arom.), 4.76 (d, *J* 14.2, 1H, PhC*H*$_2$), 4.71 (d, *J* 14.2, 1H, PhC*H*$_2$), 4.62 (dd, *J* 6.7, 1.8, 1H, *H*-9), 4.10 (dtd, *J* 11.9, 6.1, 1.8, 1H, *H*-1), 3.80 (ddd, *J* 11.9, 7.4, 5.2, 1H, *H*-1), 3.63 (ddd, *J* 8.2, 6.5, 1.2, 1H, *H*-4), 3.08 (ddd, *J* 6.5, 3.8, 2.6, 1H, *H*-7), 2.88 (dddd, *J* 18.9, 6.7, 3.8, 1.2, 1H, *H*-8), 2.31 – 2.11

(m, 2H, *H*-2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.5 (*C*-6), 172.2 (d, *J* 5.7, *C*-5), 137.8 (*C*-10), 135.4 (*C* arom.), 134.2 (*C*-13), 128.9 (*C*H arom.), 128.7 (*C*H arom.), 128.7 (*C*H arom.), 128.1 (*C*H arom.), 127.7 (*C*-11), 91.2 (d, *J* 221.5, *C*-3), 61.2 (d, *J* 6.0, *C*-1), 48.2 (d, *J* 22.3, *C*-8), 47.9 (d, *J* 23.9, *C*-4), 43.0 (Ph*C*H$_2$), 38.2 (d, *J* 5.3, *C*-7), 31.6 (d, *J* 22.5, *C*-2); **HRMS** (ESI^+) 400.1093 $[M + H]^+$ 422.0918 $[M + Na]^+$ ($C_{22}H_{20}ClFNO_3$ requires 400.1110, $C_{22}H_{19}ClFNNaO_3$ requires 422.0930).

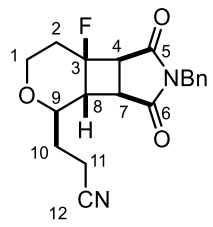
39f – (±)-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-benzyl-7a-fluoro-4-propylhexahydropyrano[3',4':3,4]cyclobuta-[1,2-c]pyrrole-1,3(2H,3aH)-dione



39f

Following general procedure B, the reaction was conducted with **16b** and butyraldehyde diethyl acetal. The product was purified by column chromatography (20% ethyl acetate/petroleum ether) and then recrystallised from ethanol to give **39f** as colourless crystals (139 mg, 72%); **m.p.** 103-104 °C (from ethanol); **IR** υ_{max}/cm^{-1} 2959, 2933, 2872, 1774, 1699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.19 (m, 5H, C*H* arom.), 4.76 (d, *J* 14.2, 1H, PhC*H*$_2$), 4.70 (d, *J* 14.2, 1H, PhC*H*$_2$), 4.08 (dtd, *J* 11.7, 5.6, 2.1, 1H, *H*-1), 3.60 (ddd, *J* 11.7, 8.3, 4.9, 1H, *H*-1), 3.54 (ddd, *J* 10.0, 6.4, 1.2, 1H, *H*-4), 3.42 (tdd, *J* 7.6, 4.9, 1.9, 1H, *H*-9), 2.81 (ddd, *J* 6.4, 3.2, 2.2, 1H, *H*-7), 2.40 (dddd, *J* 19.8, 7.6, 3.2, 1.2, 1H, *H*-8), 2.17 – 2.00 (m, 2H, *H*-2), 1.71 – 1.63 (m, 1H, *H*-11), 1.60 – 1.35 (m, 3H, *H*-11 & *H*-10), 0.96 (t, *J* 7.2, 3H, *H*-12); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.8 (*C*-6), 172.5 (d, *J* 6.5, *C*-5), 135.5 (*C* arom.), 128.6 (*C*H arom.), 128.6 (*C*H arom.), 128.0 (*C*H arom.), 92.5 (d, *J* 217.3, *C*-3), 78.2 (d, *J* 3.4, *C*-9), 61.9 (d, *J* 7.0, *C*-1), 48.0 (d, *J* 21.6, *C*-8), 47.6 (d, *J* 24.0, *C*-4), 43.0 (Ph*C*H$_2$), 38.9 (d, *J* 3.5, *C*-7), 37.0 (*C*-10), 31.7 (d, *J* 22.2, *C*-2), 18.6 (*C*-11), 14.0 (*C*-12); **HRMS** (ESI^+) 354.1493 $[M + Na]^+$ ($C_{19}H_{22}FNNaO_3$ requires 354.1476).

39g – (±)-3-((3a*S*,3b*S*,4*S*,7a*R*,7b*S*)-2-benzyl-7a-fluoro-1,3-dioxodecahydropyrano[3',4':3,4]cyclo-buta[1,2-c]pyrrol-4-yl)propanenitrile

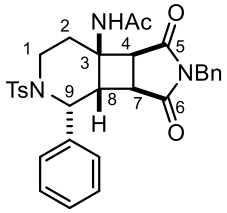


39g

Following general procedure B, the reaction was conducted with **16b** and 3-cyanopropionaldehyde diethylacetal. The product was purified by column chromatography (80% ethyl acetate/petroleum ether) to give the pure product **39g** (86.4 mg, 43%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2933, 2866, 2246, 1775, 1700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.14 (m, 5H, C*H* arom.), 4.74 (d, *J* 14.3, 1H, PhCH_2), 4.67 (d, *J* 14.3, 1H, PhCH_2), 4.06 (dtd, *J* 11.8, 5.9, 1.9, 1H, *H*-1), 3.67 (ddd, *J* 11.8, 8.0, 4.8, 1H, *H*-1), 3.61 – 3.49 (m, 2H, *H*-9 & *H*-4), 2.85 (dt, *J* 6.1, 3.0, 1H, *H*-7), 2.63 – 2.41 (m, 2H, *H*-11), 2.36 (dddd, *J* 19.4, 8.0, 3.0, 1.2, 1H, *H*-8), 2.22 – 2.00 (m, 2H, *H*-2), 1.98 – 1.77 (m, 2H, *H*-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4 (*C*-6), 172.2 (d, $^3J_{CF}$ 6.2, *C*-5), 135.4 (*C* arom.), 128.7 (*C*H arom.), 128.5 (*C*H arom.), 128.0 (*C*H arom.), 119.1 (*C*-12), 91.9 (d, $^1J_{CF}$ 218.6, *C*-3), 75.6 (d, $^3J_{CF}$ 3.5, *C*-9), 62.1 (d, $^3J_{CF}$ 6.4, *C*-1), 47.7 (d, $^2J_{CF}$ 24.0, *C*-4), 47.4 (d, $^2J_{CF}$ 22.3, *C*-8), 43.0 (Ph*C*H_2), 38.4 (d, $^3J_{CF}$ 3.7, *C*-7), 31.2 (d, $^2J_{CF}$ 22.4, *C*-2), 30.0 (*C*-10), 13.6 (*C*-11); **HRMS** (ESI^+) 365.1286 $[M + Na]^+$ ($C_{19}H_{19}FN_2NaO_3$ requires 365.1272).

4.2.4. Aza-Prins–Ritter Reactions

38a – (±)-*N*-((3a*S*,3b*R*,4*S*,7a*R*,7b*S*)-2-benzyl-1,3-dioxo-4-phenyl-5-tosyldecahydro-7aH-pyrrolo-[3',4':3,4]cyclobuta[1,2-c]pyridin-7a-yl)acetamide

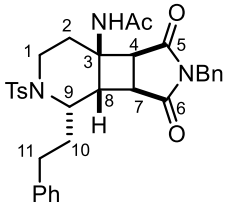


38a

Following general procedure C, the reaction was conducted with **34** and benzaldehyde. The product was purified by column chromatography (50 % ethyl acetate/petroleum ether) to give **38a** (148 mg, 68%) as a colourless solid; **m.p.** (methanol) 184-185 °C; **IR** υ_{max}/cm^{-1} 3356, 1769, 1696, 1668, 1339, 1158; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 – 7.69 (m, 2H, C*H* arom.), 7.49 – 7.20 (m, 12H, C*H* arom.), 6.00 (s, 1H, N*H*), 5.53 (d, *J* 5.5, 1H, *H*-9), 4.59 (d, *J* 14.1, 1H, PhCH_2), 4.50 (d, *J* 14.1, 1H, PhCH_2), 4.11 (dt, *J* 15.4, 3.9, 1H, *H*-1), 3.45 (ddd, *J* 15.4, 13.4, 1.8, 1H, *H*-1), 3.12 (t, *J* 6.7, 1H, *H*-7), 3.01 (dd, *J* 6.7, 1.1, 1H, *H*-4), 2.81 (dd, *J* 6.7, 5.5, 1H, *H*-8), 2.44 (s, 3H, CH_3), 1.86 (td, *J* 13.4, 3.9, 1H, *H*-2), 1.78 (s, 3H, CH_3), 1.53 (m, 1H, *H*-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.7 (*C*-6), 175.6 (*C*-5), 168.8 (*C*=O), 143.6 (*C* arom.), 140.6 (*C* arom.), 136.0 (*C* arom.), 135.4 (*C* arom.), 129.6(*C*H arom.), 128.6 (*C*H arom.), 128.6 (*C*H arom.), 128.5 (*C*H arom.), 128.1 (*C*H arom.), 127.9 (*C*H arom.), 127.5 (*C*H arom.), 126.2 (*C*H arom.), 58.3 (*C*-9), 52.4 (*C*-3), 48.8 (*C*-8), 43.8 (*C*-4), 42.7 (Ph*C*H_2), 40.8 (*C*-1), 37.2 (*C*-7),

32.6 (*C*-2), 23.2 (*C*H$_3$), 21.6 (*C*H$_3$); **HRMS** (ESI$^+$) 580.1850 [M + Na]$^+$ ($C_{31}H_{31}N_3NaO_5S$ requires 580.1877).

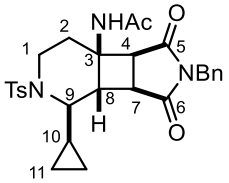
38b – (±)-*N*-((3a*S*,3b*R*,4*S*,7a*R*,7b*S*)-2-benzyl-1,3-dioxo-4-phenethyl-5-tosyldecahydro-7aH-pyrrolo-[3',4':3,4]cyclobuta[1,2-c]pyridin-7a-yl)acetamide



38b

Following general procedure C, the reaction was conducted with **34** and hydrocinnamaldehyde. Column chromatography (25% ethyl acetate/petroleum ether) gave the product **38b** (0.14 g, 83%, d.r. 5:1) as a white solid (NMR data for the major diastereomer); **m.p.** (ethanol) 109-110 °C; **IR** υ_{max}/cm^{-1} 3362, 2927, 1770, 1702; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* 8.2, 2H, C*H* arom.), 7.44 – 7.05 (m, 12H, C*H* arom.), 5.84 (s, 1H, N*H*), 4.72 (d, *J* 14.1, 1H, PhC*H*$_2$), 4.67 (d, *J* 14.1, 1H, PhC*H*$_2$), 4.18 (ddd, *J* 9.8, 5.9, 2.7, 1H, *H*-9), 3.76 (dt, *J* 15.1, 4.4, 1H, *H*-1), 3.28 (m, 1H, *H*-1), 3.22 (dd, *J* 6.8, 5.9, 1H, *H*-7), 3.03 (d, *J* 6.8, 1H, *H*-4), 2.83 (t, *J* 5.9, 1H, *H*-8), 2.65 – 2.45 (m, 3H, *H*-10 and *H*-11), 2.40 (s, 3H, C*H*$_3$), 2.00 (m, 1H, *H*-10), 1.75 (m, 1H, *H*-2), 1.69 (s, 3H, C*H*$_3$), 1.53 (ddd, *J* 13.8, 4.9, 2.5, 1H, *H*-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.0 (*C*-6), 175.6 (*C*-5), 168.8 (*C*=O), 143.5 (*C* arom.), 141.4 (*C* arom.), 136.3 (*C* arom.), 135.5 (*C* arom.), 129.7 (*C*H arom.), 128.7 (*C*H arom.), 128.7 (*C*H arom.), 128.5 (*C*H arom.), 128.3 (*C*H arom.), 127.6 (*C*H arom.), 125.9 (*C*H arom.), 54.8 (*C*-9), 52.3 (*C*-3), 45.5 (*C*-8), 44.7 (*C*-4), 42.8 (Ph*C*H$_2$), 40.7 (*C*-1), 37.3 (*C*-7), 36.4 (*C*-10), 32.6 (*C*-2), 32.0 (*C*-11), 23.2 (*C*H$_3$), 21.5 (*C*H$_3$); **HRMS** (ESI$^+$) 586.2368 [M + H]$^+$ 608.2188 [M + Na]$^+$ ($C_{33}H_{36}N_3O_5S$ requires 586.2370, $C_{33}H_{35}N_3NaO_5S$ requires 608.2190).

38c – (±)-*N*-((3a*S*,3b*R*,4*S*,7a*R*,7b*S*)-2-benzyl-4-cyclopropyl-1,3-dioxo-5-tosyldecahydro-7aH-pyrrolo-[3',4':3,4]cyclobuta[1,2-c]pyridin-7a-yl)acetamide

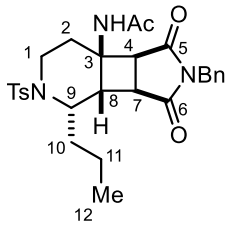


38c

Following general procedure C, the reaction was conducted with **34** and cyclopropanecarboxaldehyde. The product was purified by column chromatography (60% ethyl acetate/petroleum ether) to give **38c** (87.6 mg, 24%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3355,

2970, 1771, 1699, 1535; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (m, 2H, C*H* arom.), 7.32 (m, 7H, C*H* arom.), 5.90 (s, 1H, N*H*), 4.71 (d, *J* 14.1, 1H, PhC*H*$_2$), 4.66 (d, *J* 14.1, 1H, PhC*H*$_2$), 3.69 (m, 2H, *H*-1), 3.52 (t, *J* 6.5, 1H, *H*-7), 3.25 (dd, *J* 10.0, 5.9, 1H, *H*-9), 3.18 (dd, *J* 6.5, 1.0, 1H, *H*-4), 2.76 (dd, *J* 6.5, 5.9, 1H, *H*-8), 2.42 (s, 3H, C*H*$_3$), 2.34 (dt, *J* 14.4, 5.4, 1H, *H*-2), 1.96 (m, 1H, *H*-2), 1.74 (s, 3H, C*H*$_3$), 1.13 (m, 1H, *H*-10), 0.63 – 0.42 (m, 2H, *H*-11), 0.28 (m, 1H, *H*-11), 0.07 (ddd, *J* 10.3, 5.4, 2.8, 1H, *H*-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.3 (*C*-6), 175.4 (*C*-5), 169.6 (*C*=O), 143.1 (*C* arom.), 138.4 (*C* arom.), 135.7 (*C* arom.), 129.5 (*C*H arom.), 128.7 (*C*H arom.), 128.6 (*C*H arom.), 127.0 (*C*H arom.), 60.0 (*C*-9), 52.4 (*C*-3), 47.9 (*C*-8), 46.3 (*C*-4), 42.7 (Ph*C*H$_2$), 42.2 (*C*-1), 36.9 (*C*-7), 34.0 (*C*-2), 13.6 (*C*-10), 7.7 (*C*-11), 4.3 (*C*-11); **HRMS** (ESI^+) 544.1894 $[M + H]^+$ 522.2070 $[M + Na]^+$ ($C_{28}H_{32}N_3O_5S$ requires 522.2057, $C_{28}H_{31}N_3NaO_5S$ requires 544.1877).

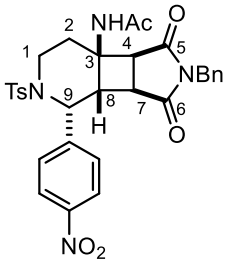
38d – (±)-*N*-((3a*S*,3b*R*,4*S*,7a*R*,7b*S*)-2-benzyl-1,3-dioxo-4-propyl-5-tosyldecahydro-7aH-pyrrolo-[3',4':3,4]cyclobuta[1,2-c]pyridin-7a-yl)acetamide



38d

Following general procedure C, the reaction was conducted with **34** and butyraldehyde. The product was purified by column chromatography (40-60% ethyl acetate/petroleum ether) to give **38d** as a colourless oil (284 mg, 78%, d.r. 4:1); **IR** υ_{max}/cm^{-1} 2966, 1702, 1393; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.72 (m, 2H, C*H* arom.), 7.37 – 7.23 (m, 7H, C*H* arom.), 5.82 (s, 1H, N*H*), 4.70 (d, *J* 14.1, 1H, PhC*H*$_2$), 4.63 (d, *J* 14.1, 1H, PhC*H*$_2$), 4.13 (ddd, *J* 9.7, 5.8, 3.8, 1H, *H*-9), 3.75 (ddd, *J* 15.0, 5.4, 4.4, 1H, *H*-1), 3.28 (ddd, *J* 15.0, 10.9, 2.9, 1H, *H*-1), 3.19 (tdd *J* 6.8, 5.8, 1H, *H*-7), 3.04 (dd, *J* 6.8, 1.1, 1H, *H*-4), 2.77 (t, *J* 5.8, 1H, *H*-8), 2.40 (s, 3H, ArC*H*$_3$), 2.16 (dddd, *J* 13.6, 10.1, 6.8, 3.8, 1H, *H*-10), 1.83 (ddd, *J* 13.9, 10.9, 4.3, 1H, *H*-2), 1.69 (s, 3H, C*H*$_3$), 1.66 (m, 1H, *H*-10), 1.55 (m, 1H, *H*-2), 1.30 – 1.19 (m, 2H, *H*-11), 0.95 – 0.88 (m, 3H, *H*-12).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.0 (*C*-6), 175.6 (*C*-5), 168.9 (*C*=O), 143.5 (*C* arom.), 136.7 (*C* arom.), 135.5 (*C* arom.), 129.7 (*C*H arom.), 128.7 (*C*H arom.), 128.5 (*C*H arom.), 128.2 (*C*H arom.), 127.5 (*C*H arom.), 54.7 (*C*-9), 52.3 (*C*-3), 45.8 (*C*-8), 44.9 (*C*-4), 42.8 (Ph*C*H$_2$), 40.7 (*C*-1), 37.2 (*C*-7), 36.0 (*C*-10), 32.6 (*C*-2), 23.2 (*C*H$_3$), 21.5 (*C*H$_3$), 19.0 (*C*-11), 13.8 (*C*-12); HRMS (ESI^+) 524.2200 $[M + H]^+$ 546.2023 $[M + Na]^+$ ($C_{28}H_{34}N_3O_5S$ requires 524.2214, C28H33N3NaO5S requires 546.2033).

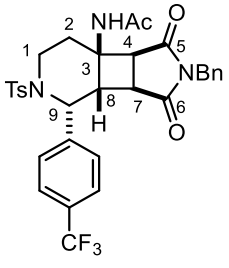
38e – (±)-*N*-((3a*S*,3b*R*,4*S*,7a*R*,7b*S*)-2-benzyl-4-(4-nitrophenyl)-1,3-dioxo-5-tosyldecahydro-7aH-pyrrolo[3',4':3,4]cyclobuta[1,2-c]pyridin-7a-yl)acetamide



38e

Following general procedure C, the reaction was conducted with **34** and *para*-nitrobenzaldehyde. The product was purified by column chromatography (40-60% ethyl acetate/petroleum ether) to give **38e** (237 mg, 56%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2969, 1705, 1519, 1346, 1065; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.26 – 8.20 (m, 2H, C*H* arom.), 7.77 – 7.73 (m, 2H, C*H* arom.), 7.66 (d, *J* 8.4, 2H, C*H* arom.), 7.47 – 7.43 (m, 2H, C*H* arom.), 7.29 – 7.18 (m, 3H, C*H* arom.), 7.14 – 7.07 (m, 2H, C*H* arom.), 5.07 (d, *J* 4.9, 1H, *H*-9), 4.35 (d, *J* 15.5, 1H, PhC*H*$_2$), 4.30 (d, *J* 15.5, 1H, PhC*H*$_2$), 3.87 (dt, *J* 15.0, 3.5, 1H, *H*-1), 3.61 (dd, *J* 15.0, 13.5, 1H, *H*-1), 3.38 (m, 1H, *H*-4), 3.28 – 3.23 (m, 2H, *H*-7 & *H*-8), 2.42 (s, 3H, C*H*$_3$) 1.95 (m, 1H, *H*-2), 1.67 (s, 3H, C*H*$_3$), 1.15 (td, *J* 13.5, 3.5, 1H, *H*-2); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 177.1 (*C*-6), 175.4 (*C*-5), 170.5 (*C*=O), 150.4 (*C* arom.), 146.8 (*C* arom.), 144.3 (*C* arom.), 136.6 (*C* arom.), 135.3 (*C* arom.), 130.5 (*C*H arom.), 128.8 (*C*H arom.), 128.3 (*C*H arom.), 128.1 (*C*H arom.), 127.8 (*C*H arom.), 127.7 (*C*H arom.), 123.8 (*C*H arom.), 56.9 (*C*-9), 53.1 (*C*-3), 46.1 (*C*-4), 45.8 (*C*-8), 42.2 (Ph*C*H$_2$), 36.0 (*C*-7), 33.0 (*C*-2), 23.4 (*C*H$_3$), 21.5 (*C*H$_3$); **HRMS** (ESI$^+$) 625.1720 $[M + Na]^+$ ($C_{31}H_{30}N_4NaO_7S$ requires 625.1727).

38f – (±)-*N*-((3a*S*,3b*R*,4*S*,7a*R*,7b*S*)-2-benzyl-1,3-dioxo-5-tosyl-4-(4-(trifluoromethyl)phenyl)deca-hydro-7aH-pyrrolo[3',4':3,4]cyclobuta[1,2-c]pyridin-7a-yl)acetamide

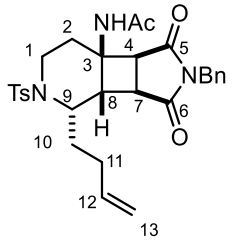


38f

Following general procedure C, the reaction was conducted with **34** and 4-(trifluoromethyl)benzaldehyde. The product was purified by column chromatography (40-60% ethyl acetate/petroleum ether) to give **38f** (134 mg, 31%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3343, 1776, 1699, 1667, 1323, 1159; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.71 (m, 4H,

C*H* arom.), 7.57 (d, *J* 8.0, 2H, C*H* arom.), 7.44 (d, *J* 7.8, 2H, C*H* arom.), 7.30 – 7.19 (m, 3H, C*H* arom.), 7.14 – 7.09 (m, 2H, C*H* arom.), 5.03 (d, *J* 5.0, 1H, *H*-9), 4.37 (d, *J* 15.1, 1H, PhC*H*$_2$), 4.32 (d, *J* 15.1, 1H, PhC*H*$_2$), 3.90 (ddd, *J* 14.0, 4.0, 3.5, 1H, *H*-1), 3.61 (t, *J* 14.0, 1H, *H*-1), 3.37 (m, 1H, *H*-4), 3.28 – 3.21 (m, 2H, *H*-7 & *H*-8), 2.42 (s, 3H, C*H*$_3$), 1.97 (d, *J* 14.0, 1H, *H*-2), 1.68 (s, 3H, C*H*$_3$), 1.18 (td, *J* 14.0, 3.5, 1H, *H*-2); **^{13}C NMR** (101 MHz, DMSO-d$_6$) δ 177.1 (*C*-6), 175.5 (*C*-5), 170.5 (*C*=O), 147.0 (*C* arom.), 144.2 (*C* arom.), 136.7 (*C* arom.), 135.5 (*C* arom.), 130.4 (*C*H arom.), 128.8 (*C*H arom.), 128.0 (*C*H arom.), 127.8 (*C*H arom.), 125.4 (*C*H arom.), 57.0 (*C*-9), 53.1 (*C*-3), 46.3 (*C*-4), 45.8 (*C*-8), 42.2 (Ph*C*H$_2$), 36.2 (*C*-7), 33.1 (*C*-2), 23.4 (*C*H$_3$), 21.5 (*C*H$_3$); **HRMS** (ESI$^+$) 626.1906 [M + H]$^+$ 648.1739 [M + Na]$^+$ ($C_{32}H_{31}F_3N_3O_5S$ requires 626.1931, $C_{32}H_{30}F_3N_3NaO_5S$ requires 648.1750).

38g – (±)-*N*-((3a*S*,3b*R*,4*S*,7a*R*,7b*S*)-2-benzyl-4-(but-3-en-1-yl)-1,3-dioxo-5-tosyldecahydro-7aH-pyrrolo[3',4':3,4]cyclobuta[1,2-c]pyridin-7a-yl)acetamide



38g

Following general procedure C, the reaction was conducted with **34** and 4-pentenal. The product was purified by column chromatography (50% ethyl acetate/petroleum ether) to give **38g** (126 mg, 60%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3355 (w), 2254 (w), 1770 (w), 1698, 1668, 1338, 1157; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.76 – 7.71 (m, 2H, C*H* arom.), 7.36 – 7.26 (m, 7H, C*H* arom.), 5.86 (s, 1H, N*H*), 5.79 (ddt, *J* 17.0, 10.1, 6.9, 1H, *H*-12), 5.03 – 4.90 (m, 2H, *H*-13), 4.70 (d, 1H, *J* 14.0, PhC*H*$_2$), 4.65 (d, 1H, *J* 14.0, PhC*H*$_2$), 4.16 (ddd, *J* 9.6, 5.5, 3.7, 1H, *H*-9), 3.75 (ddd, *J* 15.1, 5.1, 4.2, 1H, *H*-1), 3.27 (ddd, *J* 15.1, 11.3, 2.7, 1H, *H*-1), 3.19 (t, *J* 6.7, 1H, *H*-7), 3.04 (dd, *J* 6.7, 1.1, 1H, *H*-4), 2.78 (ddd, *J* 6.7, 5.5, 1.0, 1H, *H*-8), 2.41 (s, 3H, C*H*$_3$), 2.32 (dddd, *J* 13.3, 9.6, 7.0, 3.7, 1H, *H*-10), 2.08 – 1.88 (m, 2H, *H*-11), 1.81 – 1.63 (m, 2H, *H*-2 & *H*-10), 1.69 (s, 3H, C*H*$_3$), 1.55 (m, 1H, *H*-2); **^{13}C NMR** ($CDCl_3$) δ 176.9 (*C*-6), 175.6 (*C*-5), 168.9 (*C*=O), 143.5 (*C* arom.), 137.4 (*C*-12), 136.5(*C* arom.), 135.5 (*C* arom.), 129.7 (*C*H arom.), 128.7 (*C*H arom.), 128.5 (*C*H arom.), 128.2 (*C*H arom.), 127.6 (*C*H arom.), 115.4 (*C*-13), 54.4 (*C*-9), 52.3 (*C*-3), 45.4 (*C*-8), 44.8 (*C*-4), 42.7 (Ph*C*H$_2$), 40.7 (*C*-1), 37.2 (*C*-7), 33.3 (*C*-10), 32.6 (*C*-2), 29.1 (*C*-11), 23.1 (*C*H$_3$), 21.5 (*C*H$_3$); **HRMS** (ESI$^+$) 558.2020 [M + Na]$^+$ ($C_{29}H_{33}N_3NaO_5S$ requires 558.2033).

4.3. Design of Experiments

General Procedure for DoE Experiments:

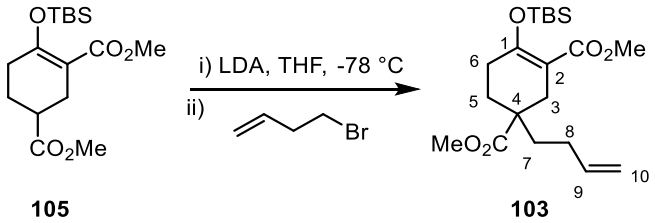
Reactions were carried out in an Integrity10 with temperature set to 25 °C and stirring at 800 rpm. Amounts were varied based on the design (Table 11). Benzaldehyde and triflic acid were dissolved in acetonitrile (2 mL) and then a solution of **1** in acetonitrile was added dropwise at the required rate. After stirring for 5 min, a sample of the reaction mixture (250 µL) was taken, concentrated, and redissolved in CD_3CN. A known amount of TCNB was added as a standard to calculate yield. The remaining reaction mixture was worked up following General Procedure A.

Table 11 – Raw data from Design 1 and 2

	Std Order	Run Order	Benzaldehyde charge / equiv.	Triflic acid excess *w.r.t.* benzaldehyde / equiv.	Addition rate of **16b** / equiv. min^{-1}	**22b** (%)	**16b** (%)	**24** (%)	**28** (%)
Design 1	1	10	1.20	0.10	0.04	76	1	0	0
	2	6	5.00	0.10	0.04	51	7	0	4
	3	4	1.20	1.00	0.04	73	5	0	17
	4	3	5.00	1.00	0.04	48	6	0	6
	5	2	1.20	0.10	0.71	73	2	0	5
	6	8	5.00	0.10	0.76	21	15	0	30
	7	1	1.20	1.00	0.79	72	2	0	8
	8	7	5.00	1.00	0.74	27	8	0	17
	9	9	3.10	0.55	0.41	43	0	0	32
	11	11	3.10	0.55	0.42	20	12	0	29
	12	12	3.10	0.55	0.42	34	23	0	14
Design 2	1	5	1.02	-0.90	0.73	7	72	5	0
	2	3	1.20	-0.90	0.76	17	64	7	2
	3	4	1.02	0.00	0.76	79	3	0	4
	4	6	1.20	0.00	0.73	73	1	0	4
	5	1	1.11	-0.45	0.72	37	34	10	2
	6	2	1.11	-0.45	0.77	36	30	10	2
	7	7	1.11	-0.45	0.74	43	29	10	2
	8	8	1.11	-0.45	0.76	35	12	21	0
	9	10	1.02	-0.90	0.04	8	34	25	0
	10	14	1.20	-0.90	0.04	27	40	27	0
	11	11	1.02	0.00	0.04	69	2	7	4
	12	12	1.20	0.00	0.04	59	0	8	1
	13	9	1.11	-0.45	0.40	41	5	23	2
	14	13	1.11	-0.45	0.40	45	18	18	2

4.4. Experimental Procedures for Chapter 3

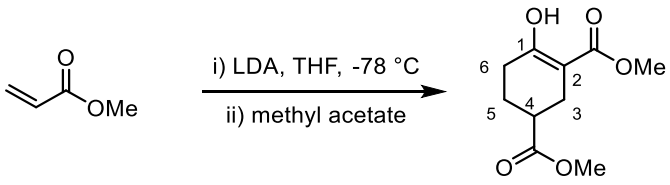
103 – (±)-Dimethyl 4-(but-3-en-1-yl)-1-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-ene-2,4-dicarboxy-late



105 **103**

105 (100 mg, 0.30 mmol) was added to a solution of LDA (0.30 mmol) in THF (2 mL) at -78 °C and stirred for 30 min forming a bright red solution. 4-Bromo-1-butene (34 µL, 0.30 mmol) was then added dropwise and the solution stirred at -78 °C for 30 min before warming to room temperature. After 4.5 h, the solution was quenched with ice cold water (1.0 mL) and hydrochloric acid (1.0 M, 1.0 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography (3% ethyl acetate/petroleum ether) to give the pure product **103** (40 mg, 35%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2951, 2930, 1857, 1726, 1694, 1661, 1639; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.75 (ddt, *J* 16.9, 10.0, 6.5, 1H, *H*-9), 4.99 (dq, *J* 16.9, 2.0, 1H, *H*-10), 4.94 (ddt, *J* 10.0, 2.0, 1.2, 1H, *H*-9), 3.69 (s, 3H, -OC*H*$_3$), 3.65 (s, 3H, -OC*H*$_3$), 2.92 (d, *J* 16.9, 1H, *H*-3), 2.41 – 1.90 (m, 5H, *H*-3,5,8,7), 1.73 – 1.53 (m, 4H, *H*-5,6,7), 0.93 (s, 9H, -OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.15 (s, 3H, -OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.13 (s, 3H, -OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.1 (*C*=O), 167.6 (*C*=O), 158.5 (*C*-1), 137.9 (*C*-9), 114.8 (*C*-10), 107.0 (*C*-2), 51.8 (-O*C*H$_3$), 51.0 (-O*C*H$_3$), 44.7 (*C*-4), 37.8 (*C*-6), 33.3 (*C*-3), 29.7 (*C*-7), 29.7 (*C*-5), 28.7 (*C*-8), 25.7 (-OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 18.3 (-OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), -3.9 (-OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$); **HRMS** (ESI$^+$) 405.2081 [M + Na]$^+$ ($C_{20}H_{34}NaO_5Si$ requires 405.2068).

104a – (±)-Dimethyl-1-hydroxycyclohex-2-ene-2,4-dicarboxylate

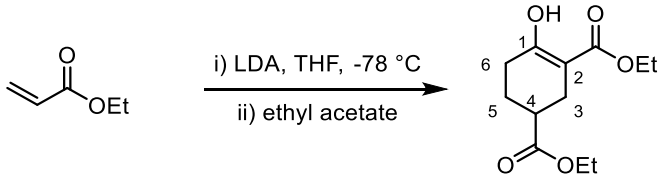


104a

Diisopropylamine (10.6 mL, 7.66 g, 75.7 mmol) was added to THF (40 mL) under a nitrogen atmosphere and cooled to 0 °C. *n*-Butyllithium (2.5 M in hexanes, 31.8 mL, 79.5 mmol,) was added dropwise and stirred for 1.5 h before cooling to -78 °C. Methyl acetate (6.0 mL, 5.60 g, 75.7 mmol) was added and the solution stirred for 45 min at -78 °C. A solution of methyl

acrylate (14.3 mL, 13.7 g, 158.9 mmol) in THF (10 mL) was added dropwise and the resulting solution stirred at -78 °C. After 1.5 h the reaction was quenched with saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine, dried with magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield the crude product as a pale-yellow oil. The product was purified by column chromatography (5-10% ethyl acetate/petroleum ether) to give the pure product **104a** (2.73 g, 17%) as a colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.13 (s, 1H, -O*H*), 3.75 (s, 3H, -OC*H*$_3$), 3.69 (s, 3H, -OC*H*$_3$), 2.59 – 2.43 (m, 2H, *H*-5 & *H*-4), 2.40 – 2.36 (m, 3H, *H*-5 & *H*-6), 2.06 (m, 1H, *H*-3), 1.79 (m, 1H, *H*-3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.0 (*C*=O), 172.5 (*C*=O), 171.1 (*C*-1), 96.1 (*C*-2), 51.8 (-O*C*H$_3$), 51.49 (-O*C*H$_3$), 39.0 (*C*-4), 28.1 (*C*-6), 24.8 (*C*-5), 24.1 (*C*-3); **HRMS** (ESI$^+$) 215.0922 $[M + H]^+$, 237.0745 $[M + Na]^+$ ($C_{10}H_{15}O_5$ requires 215.0914, $C_{10}H_{14}NaO_5$ requires 218.0788). Data in accordance with literature.[158]

104b – (±)-Diethyl-1-hydroxycyclohex-2-ene-2,4-dicarboxylate

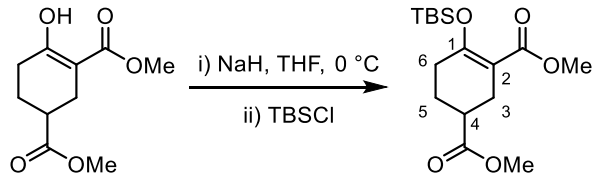


104b

Diisopropylamine (14.0 mL, 10.1 g, 100 mmol) was added to THF (65 mL) under a nitrogen atmosphere and cooled to 0 °C. *n*-Butyllithium (2.5 M in hexanes, 42 mL, 105 mmol) was added dropwise and stirred for 1.5 h before cooling to -78 °C. Ethyl acetate (9.8 mL, 8.8 g, 100 mmol) was added and the solution stirred for 45 min at -78 °C. A solution of ethyl acrylate (22.4 mL, 21.0 g, 210 mmol) in THF (20 mL) was added dropwise and the resulting solution stirred at -78 °C. After 1.5 h the reaction was quenched with saturated ammonium chloride solution (30 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried with magnesium sulfate, filtered and the solvent removed under reduced pressure to yield the crude product as a colourless oil. The product was purified by column chromatography (5% ethyl acetate/petroleum ether) to give a 1:1 mixture of keto/enol tautomers of the product **104b** as a colourless oil (77%, 18.6 g); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.17 (s, 1H, O*H*), 4.15 (q, *J* 7.1, 2H, C*H*$_2$CH$_3$), 4.09 (q, *J* 7.1, 2H, C*H*$_2$CH$_3$), 2.56 – 2.42 (m, 2H, *H*-3 & *H*-4), 2.37 – 2.26 (m, 3H, *H*-3 & *H*-6), 1.99 (m, 1H, *H*-5), 1.73 (m, 1H, *H*-5), 1.24 (t, *J* 7.1, 3H, CH$_2$C*H*$_3$), 1.20 (t, *J* 7.1, 3H, CH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.7 (*C*=O), 172.3 (*C*=O), 171.0 (*C*-1), 96.3 (*C*-2), 60.6 (*C*H$_2$CH$_3$), 60.4 (*C*H$_2$CH$_3$), 39.3 (*C*-4), 28.2 (*C*-6), 24.8 (*C*-3), 24.3 (*C*-5), 14.3 (CH$_2$*C*H$_3$), 14.2 (CH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 243.1231 $[M + H]^+$

265.1055 [M + Na] ($C_{12}H_{19}O_5$ requires 243.1227, $C_{12}H_{18}NaO_5$ requires 265.1046). Data in accordance with literature.[158]

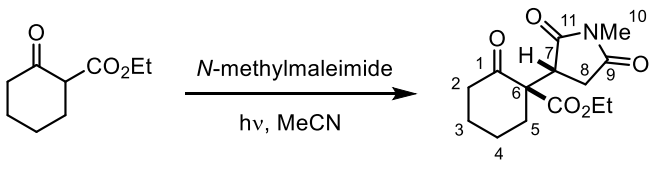
105 – (±)-Dimethyl 1-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-ene-2,4-dicarboxylate



104a **105**

A solution of **104a** (1.86 g, 8.53 mmol) in THF (10 mL) was added dropwise to a cooled suspension of sodium hydride (60% dispersion in mineral oil, 0.51 g, 12.8 mmol) at 0 °C. After 1 h, *tert*-butyldimethylsilylchloride (1.9 g, 12.8 mmol) was added at 0 °C and the solution then warmed to room temperature and stirred for 23 h. After this time, the reaction was quenched with saturated sodium hydrogen carbonate solution (5 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography (5% ethyl acetate/petroleum ether) to give the product **105** (1.6 g, 58%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2953, 2857, 1734, 1660, 1619; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.69 (s, 3H, -OC*H*$_3$), 3.68 (s, 3H, -OC*H*$_3$), 2.67 (m, 1H, *H*-3), 2.53 – 2.49 (m, 2H, *H*-4 & *H*-3), 2.28 – 2.24 (m, 2H, *H*-6), 1.99 (m, 1H, *H*-5), 1.79 (m, 1H, *H*-5), 0.94 (s, 9H, -OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.16 (s, 3H, -OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.16 (s, 3H, -OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.1 (*C*-1), 167.6 (C=O), 158.5 (C=O), 107.1 (*C*-2), 51.8 (O-CH$_3$), 51.1 (O-CH$_3$), 38.9 (*C*-4), 31.2 (*C*-6), 27.8 (*C*-5), 25.7 (-OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 24.9 (*C*-3), 18.3 (-OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), -3.8 (-OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$); **HRMS** (ESI$^+$) 351.1611 [M + Na]$^+$ ($C_{16}H_{28}NaO_5Si$ requires 351.1598).

109 – (±)-(6*R*,7*R*)-Ethyl 6-(1-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxocyclohexane-6-carboxylate

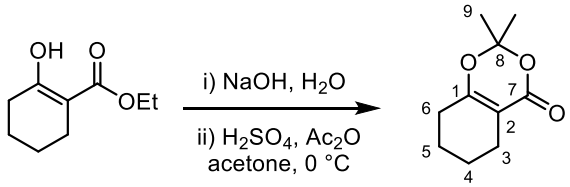


106 **109**

Ethyl 2-oxocyclohexanecarboxylate (1.8 mL, 1.9 g, 11.25 mmol) and *N*-methylmaleimide (0.83 g, 7.5 mmol) were dissolved in degassed acetonitrile (150 mL) and irradiated (125 W, medium pressure Hg lamp). After 2 h the solvent was removed under reduced pressure to give a milky white oil. The crude product was purified by column chromatography (20-50% ethyl acetate/petroleum ether) to give the pure product **109** (0.67 g, 33%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2942, 2867, 1776, 1726, 1694; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.40 – 4.20 (m,

2H, -OC*H*$_2$CH$_3$), 3.17 (dd, *J* 9.4, 5.9, 1H, *H*-7), 2.99 (s, 3H, *H*-10), 2.85 (m, 1H, *H*-2), 2.76 (dd, *J* 17.8, 9.4, 1H, *H*-8), 2.49 – 2.45 (m, 2H, *H*-2 & *H*-5), 2.31 (dd, *J* 17.8, 5.9, 1H, *H*-8), 2.06 (m, 1H, *H*-3), 1.81 (m, 1H, *H*-4), 1.68 – 1.64 (m, 3H, *H*-3, *H*-4 & *H*-5), 1.31 (t, *J* 7.2, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 206.8 (*C*-1), 177.4 (*C*-11), 175.7 (*C*-9), 171.2 (*C*=O), 62.7 (*C*-6), 62.2 (-OC*H*$_2$CH$_3$), 44.4 (*C*-7), 40.7 (*C*-2), 35.9 (*C*-5), 32.4 (*C*-8), 26.5 (*C*-3), 24.8 (*C*-10), 21.6 (*C*-4), 14.0 (-OCH$_2$C*H*$_3$); **HRMS** (ESI$^+$) 282.1340 [M + H]$^+$, 304.1161 [M + Na]$^+$ ($C_{14}H_{20}NO_5$ requires 282.1336, $C_{14}H_{19}NNaO_5$ requires 304.1155).

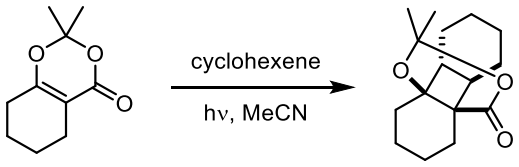
112 – 8,8-Dimethyl-3,4,5,6-tetrahydro-4H-benzo[d][1,3]dioxin-2-one



106 **112**

Ethyl 2-oxocyclohexanecarboxylate (2.00 mL, 2.13 g, 12.5 mmol) was added to a solution of sodium hydroxide (1.0 M, 20 mL) at 0 °C resulting in the formation of a white precipitate. After 18 h, the resulting clear orange solution was washed with diethyl ether (3 × 20 mL) and the aqueous layer acidified with hydrochloric acid at 0 °C and stirred to form a pale-yellow slurry. Filtration afforded the carboxylic acid as a white solid. 2-Oxocyclohexanecarboxylic acid (0.57 g, 4.0 mmol) was dissolved in acetone (0.6 mL) and acetic anhydride (0.8 mL) and cooled to -5 °C. Concentrated sulphuric acid (0.05 mL) was added dropwise and the solution stirred at 0 °C for 4.5 h. After this time the reaction was quenched with saturated sodium hydrogen carbonate solution (2 mL) and then extracted with diethyl ether (3 × 10 mL), dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield the dioxenone **112** (0.51 g, 24%) as a pale yellow oil; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 2.30 (tt, *J* 6.0, 1.9, 2H, *H*-3/6), 2.19 (tt, *J* 6.2, 1.9, 2H, *H*-6/3), 1.79 – 1.63 (m, 4H, *H*-4 & *H*-5), 1.67 (s, 6H, *H*-9); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 164.9 (*C*-1), 162.2 (*C*-7), 105.2 (*C*-8), 102.3 (*C*-2), 27.5 (*C*-3/6), 25.1 (*C*-9), 22.0 (*C*-4/5), 21.7 (*C*-4/5), 21.2 (*C*-3/6). **HRMS** (ESI$^+$) 183.1014 [M + H]$^+$ ($C_{10}H_{15}O_3$ requires 183.1016). Data in accordance with literature.[166]

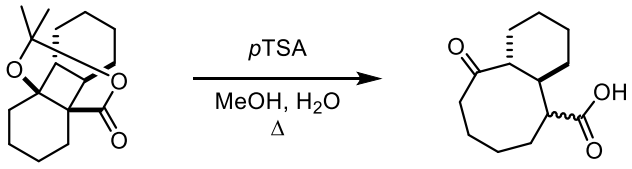
113 – (±)-11,11-Dimethyldecahydro-4a,8b-(epoxymethanooxymethano)biphenylen-9-one



112 **113**

Dioxenone **112** (0.27 g, 1.5 mmol) and cyclohexene (0.15 mL, 0.12 g, 1.5 mmol) were dissolved in degassed acetonitrile (150 mL) and irradiated (125 W, medium pressure Hg lamp). After 1 h, no reaction progression was observed so a further 9 equivalents (1.3 mL) of cyclohexene was added. After 2 h, the reaction was complete, and the solvent removed under reduced pressure. The resulting yellow oil was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the pure product **113** (0.325 g, 82%) as a white solid which was recrystallised from methanol to give colourless cubic crystals; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.67 (m, 1H, C*H*), 2.19 (m, 1H, C*H*), 1.92 – 1.66 (m, 7H, CH_2), 1.65 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.58 – 1.00 (m, 9H, CH_2); **HRMS** (ESI^+) 287.1629 $[M + Na]^+$ ($C_{16}H_{24}NaO_3$ requires 287.1618).

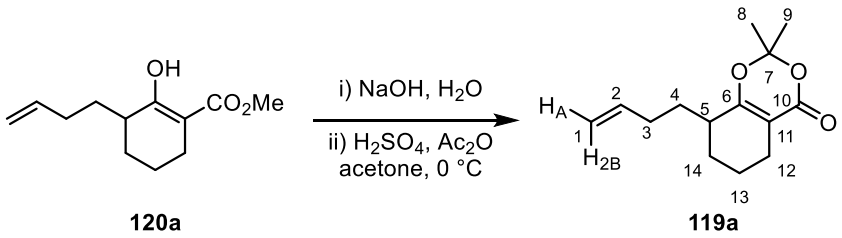
114 – (±)-10-Oxododecahydrobenzo[8]annulene-5-carboxylic acid



113 **114**

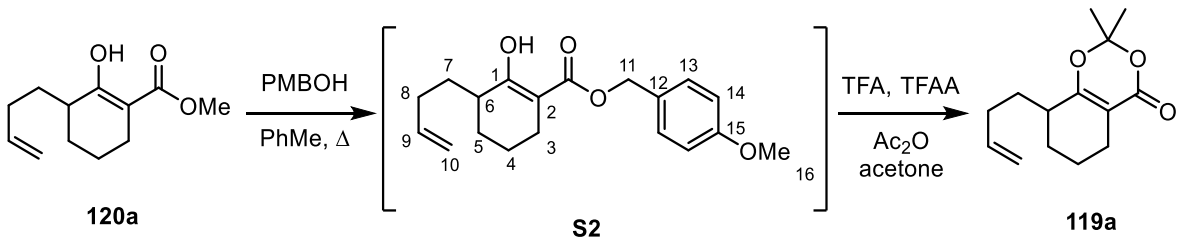
113 (250 mg, 0.95 mmol) was dissolved in methanol (9.0 mL) and water (1.0 mL). *p*TSA (18 mg, 0.095 mmol) added and the reaction mixture was heated at reflux for 6 h. After cooling to room temperature, the organic solvent was removed under reduced pressure and the resulting aqueous phase extracted with diethyl ether (3 × 10 mL), the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give the crude product **114** (0.167 g, 78%) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.62 – 0.95 (m, 19H, CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 219.9 (*C*=O), 181.8 (*C*=O), 54.6 (*C*H), 50.5 (*C*H), 40.3 (*C*H_2), 32.0 (*C*H), 30.0 (*C*H_2), 27.5 (*C*H_2), 26.6 (*C*H_2), 25.9 (*C*H_2), 25.5 (*C*H_2), 24.9 (*C*H_2), 24.8 (*C*H_2); **HRMS** (ESI^+) 247.1317 $[M + Na]^+$ ($C_{13}H_{20}NaO_3$ requires 247.1305).

119a – (±)-8-(But-3-en-1-yl)-2,2-dimethyl-5,6,7,8-tetrahydro-4H-benzo[d][1,3]dioxin-4-one



120a (0.9 g, 4.0 mmol) was added dropwise to a solution of sodium hydroxide (1.0 M, 10 mL) at 0 °C. The resulting suspension was allowed to warm to room temperature overnight. After 18 h the resulting yellow solution was washed with diethyl ether (3 × 10 mL) and the aqueous layer acidified with hydrochloric acid (3.0 M) at 0 °C forming a cream precipitate which was isolated by filtration. The resulting solid (0.29 g, 1.5 mmol) was dissolved in acetone (0.45 mL) and acetic anhydride (0.31 mL, 0.33 g, 3.25 mmol) and cooled to -5 °C. Concentrated sulfuric acid (0.02 mL, 0.37 mmol) was added dropwise and the resulting solution stirred at 0 °C for 4 h. The reaction was quenched with sodium hydrogen carbonate (2 mL), extracted with diethyl ether (3 × 5 mL) and the organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography (5 % ethyl acetate/petroleum ether) to give the pure product **119a** (0.15 g, 16%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2939, 2858, 1725, 1643; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.76 (ddt, *J* 17.1, 10.2, 6.6, 1H, *H*-2), 5.01 (dq, *J* 17.1, 2.0, 1H, *H*-1_B), 4.96 (dq, *J* 10.2, 2.0, 1H. *H*-1_A), 2.26 – 2.23 (m, 3H, *H*-5 & *H*-12), 2.14 (m, 1H, *H*-3), 2.04 (m, 1H, *H*-3), 1.78 – 1.73 (m, 2H, *H*-4 & *H*-14), 1.68 (m, 1H, *H*-13), 1.62 (s, 3H, *H*-8/9), 1.61 (s, 3H, *H*-8/9), 1.54 – 1.50 (m, 2H, *H*-13 & *H*-14), 1.38 (dtd, *J* 13.5, 9.3, 5.3, 1H, *H*-4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.0 (*C*-6), 162.2 (*C*-10), 137.7 (*C*-2), 115.1 (*C*-1), 105.0 (*C*-7), 102.5 (*C*-11), 36.3 (*C*-5), 31.2 (*C*-3), 30.4 (*C*-4), 26.7 (*C*-14), 25.4 (*C*-8/9), 24.8 (*C*-8/9), 21.6 (*C*-12), 19.5 (*C*-13); **HRMS** (ESI^+) 237.1490 $[M + H]^+$, 259.1308 $[M + Na]^+$ ($C_{14}H_{21}O_3$ requires 237.1485, $C_{14}H_{20}NaO_3$ requires 259.1305).

119a – (±)-2-Methoxybenzyl 6-(but-3-en-1-yl)-1-hydroxycyclohex-2-ene-2-carboxylate

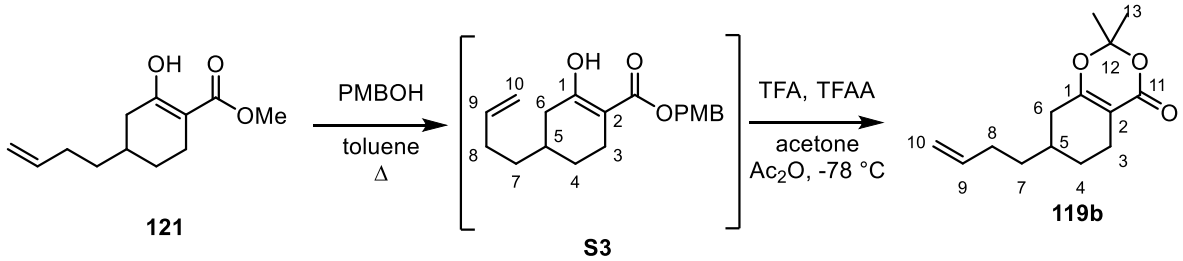


120a (1.00 g, 4.76 mmol) and *p*-methoxybenzyl alcohol (1.77 mL, 1.97 g, 14.3 mmol) were dissolved in dry toluene (20 mL) and heated at reflux with a Dean-Stark trap for removal of

methanol. After 48 h, the solvent was removed under reduced pressure to give an orange oil. The crude product was purified by column chromatography (5-10% diethyl ether/petroleum ether) to give the pure product **S2** (1.10 g, 73%) as a colourless oil; Data in accordance with previous procedure. **IR** υ_{max}/cm^{-1} 2936, 2862, 1742, 1712, 1642, 1611, 1514; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.35 (s, 1H, OH), 7.32 – 7.27 (m, 2H, *H*-13), 6.92 – 6.86 (m, 2H, *H*-14), 5.77 (m, 1H, *H*-9), 5.13 (d, *J* 1.4, 2H, *H*-11), 6.02 – 5.96 (m, 2H, *H*-10), 3.80 (s, 3H, *H*-16), 3.41 (m, 1H, *H*-2'), 2.55 – 1.22 (m, 10H, *H*-3,4,5,7 & 8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.1 (*C*-1'), 175.0 (*C*-1), 159.6 (*C*-15), 138.4 (*C*-9), 129.8 (*C*-13), 128.2 (*C*-12), 114.8 (*C*-10), 113.9 (*C*-14), 97.7 (*C*-2), 65.6 (*C*-11), 56.2 (*C*-2'), 55.2 (*C*-16), 37.9 (*C*-6), 31.2 (*C*-7), 31.0 (*C*-8), 27.0 (*C*-3/4/5), 22.8 (*C*-3/4/5), 20.0 (*C*-3/4/5); **HRMS** (ESI^+) 339.1580 $[M + Na]^+$ ($C_{19}H_{24}NaO_4$ requires 339.1567).

S2 (1.18 g, 3.73 mmol) was dissolved in dry acetone (15.0 mL) and cooled to -78 °C. TFAA (4.90 g, 23.3 mmol, 3.24 mL) was added dropwise, followed by acetic anhydride (2.71 g, 26.6 mmol, 2.51 mL) and TFA (15.0 mL) before stirring at -78 °C for 2.5 h and then at room temperature for 16 h. The reaction mixture was added dropwise to saturated sodium hydrogen carbonate (ca. 50 mL) and solid sodium hydrogen carbonate added until neutral. The aqueous solution was extracted with ethyl acetate (3 × 50 mL), washed with brine (100 mL) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (5% diethyl ether/petroleum ether) to give **119a** (0.35 g, 40%) as a colourless oil. Analytical data provided on page 145.

119b – (±)-5-(But-3-en-1-yl)-12,12-dimethyl-3,4,5,6-tetrahydro-4H-benzodioxin-2-one

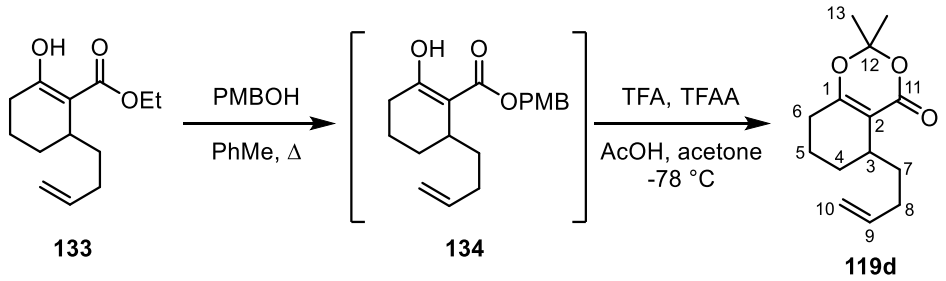


121 (0.90 g, 4.30 mmol) and *p*-methoxybenzyl alcohol (1.77 g, 12.8 mmol) were dissolved in toluene (25 mL) and heated at reflux with a Dean-Stark trap. After 18 h, the reaction was cooled to room temperature and the solvent removed under reduced pressure. The product was purified by column chromatography (5% diethyl ether/petroleum ether) to give **S3** (1.00 g, 74%) as a colourless oil. Isolated as a 2:3 mixture of keto/enol tautomers, NMR data given for major enol tautomer. **IR** υ_{max}/cm^{-1} 2922, 2853, 1656, 1616, 1275, 1214; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.15 (s, 1H, O*H*), 7.37 – 7.28 (m, 2H, C*H* arom.), 6.91 (dd, *J* 8.8, 3.1, 2H, C*H*

arom.), 5.81 (m, 1H, *H*-9), 5.16 (s, 2H, C*H*$_2$), 5.06 – 4.98 (m, 2H, *H*-10), 3.83 (s, 3H, -OC*H*$_3$), 2.40 – 2.35 (m, 2H, *H*-4, *H*-6), 2.28 – 1.93 (m, 4H, *H*-4, *H*-8, *H*-6), 1.78 (m, 1H, *H*-3), 1.68 (m, 1H, *H*-5), 1.48 – 1.39 (m, 2H, *H*-7), 1.22 (m, 1H, *H*-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4 (*C*-1), 171.8 (*C*=O), 159.6 (*C* arom.) 138.5 (*C*-9), 129.8 (*C*H arom.), 128.2 (*C* arom.) 114.6 (*C*-10), 113.9 (*C*H arom.), 97.5 (*C*-2), 65.6 (*C*H$_2$), 55.3 (-O*C*H$_3$), 35.4 (*C*-6), 35.0 (*C*-7), 32.6 (*C*-5), 31.0 (*C*-8), 28.4 (*C*-3), 22.0 (*C*-4); **HRMS** (ESI$^+$) 339.1572 $[M + Na]^+$ ($C_{19}H_{24}NaO_4$ requires 339.1567).

S3 (1.00 g, 3.20 mmol) was dissolved in dry acetone (13.5 mL) and cooled to -78 °C. TFAA (4.16 g, 19.8 mmol, 2.75 mL) was added dropwise, followed by acetic anhydride (2.31 g, 22.6 mmol, 2.14 mL) and TFA (13.5 mL) before stirring at -78 °C for 2.5 h and then at room temperature for 16 h. The reaction mixture was added dropwise to saturated sodium hydrogen carbonate (ca. 50 mL) and solid sodium hydrogen carbonate added until neutral. The aqueous solution was extracted with ethyl acetate (3 × 50 mL), washed with brine (100 mL) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (5% diethyl ether/petroleum ether) to give **119b** (0.30 g, 42%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3002, 2925, 2861, 1725, 1655, 1403; **^{1}H NMR** (400 MHz, $CDCl_3$) 5.82 (ddt, J 17.1, 10.1, 6.7, 1H, *H*-9), 5.05 (dd, *J* 17.1, 1.6, 1H, *H*-10), 5.00 (dd, *J* 10.1, 1.6, 1H, *H*-10), 2.45 (m, 1H, *H*-3), 2.31 (dd, *J* 18.3, 5.1, 1H, *H*-6), 2.23 (m, 1H, *H*-3), 2.17 – 2.09 (m, 2H, *H*-8), 1.94 – 1.86 (m, 2H, *H*-4 & *H*-6), 1.74 (m, 1H, *H*-5), 1.68 (s, 3H, *H*-13), 1.67 (s, 3H, *H*-13), 1.49 – 1.40 (m, 2H, *H*-7), 1.26 (m, 1H, *H*-4); **^{13}C NMR** (101 MHz, $CDCl_3$) 164.3 (*C*-11), 162.0 (*C*-1), 138.3 (*C*-9), 114.9 (*C*-10), 105.3 (*C*-12), 102.1 (*C*-2), 34.8 (*C*-7), 33.8 (*C*-6), 32.7 (*C*-5), 31.0 (*C*-8), 28.1 (*C*-4), 26.0 (*C*-13), 24.3 (*C*-13), 20.8 (*C*-3); **HRMS** (ESI$^+$) 259.1313 $[M + Na]^+$ ($C_{14}H_{20}NaO_3$ requires 259.1305).

119d – (±)-3-(But-3-en-1-yl)-12,12-dimethyl-3,4,5,6-tetrahydro-4H-benzodioxin-2-one



133 **134** **119d**

133 (150 mg, 0.71 mmol) and *p*-methoxybenzyl alcohol (296 mg, 2.14 mmol) were dissolved in toluene (5 mL) and heated at reflux with a Dean-Stark trap. After 65 h, the reaction was cooled to room temperature and the solvent removed under reduced pressure. The product was purified by column chromatography to give the *p*-methoxybenzyl ester **134** (83 mg, 37%) as a

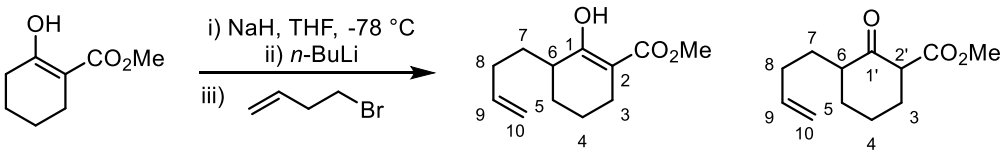
colourless oil. **134** (80 mg, 0.26 mmol) was then dissolved in dry acetone (1.5 mL) and cooled to -78 °C. TFAA (0.34 g, 1.64 mmol, 0.23 mL), TFA (1.5 mL) and acetic anhydride (0.19 g, 1.87 mmol, 0.18 mL) were added dropwise and the reaction stirred at -78 °C for 4 h before warming to room temperature overnight. After 16 h, the reaction mixture was added dropwise to saturated sodium hydrogen carbonate solution (10 mL) and solid sodium hydrogen carbonate was added until neutral. The aqueous solution was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (5% diethyl ether/petroleum ether) to give **119d** (23 mg, 37%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2929, 1722, 1511, 1247; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* 17.0, 10.2, 6.6, 1H, *H*-9), 4.96 (dq *J* 17.1, 1.7, 1H, *H*-10), 4.88 (dq, *J* 10.2, 1.7, 1H, *H*-10), 2.56 (m, 1H, *H*-3), 2.17 – 2.06 (m, 4H, *H*-6 & *H*-8), 1.81 – 1.74 (m, 2H, *H*-5 & *H*-7), 1.58 (s, 3H, *H*-13), 1.58 (s, 3H, *H*-13), 1.59 – 1.51 (m, 3H, *H*-5 & *H*-4), 1.28 (dtd, *J* 14.8, 9.8, 5.1, 1H, *H*-7); **^{13}C NMR** (101 MHz, $CDCl_3$) 165.2 (*C*-1), 161.4 (*C*-11), 138.7 (*C*-9), 114.5 (*C*-10), 106.8 (*C*-2), 104.8 (*C*-12), 33.1 (*C*-7), 31.6 (*C*-8), 31.1 (*C*-3), 27.7 (*C*-6), 26.5 (*C*-13), 26.2 (*C*-4), 23.6 (*C*-13), 18.3 (*C*-5); **HRMS** (ESI^+) 237.1484 $[M + H]^+$ ($C_{14}H_{21}O_3$ requires 237.1485).

S4 — Methyl 2-oxocyclohexane-1-carboxylate

S4

Sodium hydride (60% dispersion in mineral oil, 10 g, 250 mmol) and dimethyl carbonate (16.8 mL, 18.0 g, 200 mmol) were dissolved in THF (70 mL) and heated at reflux. A solution of cyclohexanone (8.24 mL, 7.8 g, 80 mmol) in THF (20 mL) was added dropwise over 1 h and then stirred at reflux for a further 1 h. The reaction was cooled to 0 °C and quenched with acetic acid (3.0 M, 50 mL), poured into brine (100 mL) and extracted with DCM (3 × 75 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent remove under reduced pressure to give the pure product **S4** as a colourless oil (12.5 g, quant.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.15 (s, 1H, -O*H*), 3.74 (s, 3H, -OCH_3), 2.46 – 2.15 (m, 4H, CH_2), 1.83 – 1.58 (m, 4H, CH_2). Data in accordance with literature.[209]

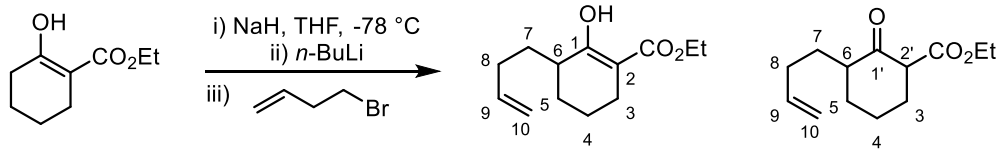
120a – (±)-Methyl 3-(but-3-en-1-yl)-2-oxocyclohexane-1-carboxylate



120a

A suspension of sodium hydride (60% dispersion in mineral oil, 2.56 g, 64.0 mmol) in dry THF (100 mL) was cooled to 0 °C. A solution of methyl 2-oxocyclohexane-1-carboxylate **S2** (5.0 g, 32.0 mmol) in dry THF (10 mL) was added dropwise over 10 min and then stirred at 0 °C for 1 h. A solution of *n*-butyllithium (2.5 M in hexanes, 20.5 mL) was added dropwise and stirred at 0 °C for 45 min before adding a solution of 4-bromobut-1-ene (2.13 mL, 2.84 g, 32.0 mmol) in dry THF (7 mL). The reaction mixture was stirred at 0 °C for a further 2 h before warming to room temperature. After 18 h, the reaction was quenched with water (50 mL), extracted with DCM (3 × 50 mL) and the combined organic extracts dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give a yellow oil. The crude product was purified by column chromatography (2% ethyl acetate/petroleum ether) to give a 1:1 mixture of the keto/enol tautomers of **120a** (1.16 g, 17%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2938, 2865, 1747, 1713, 1653, 1612; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.33 (s, 0.5H, O*H*), 5.78 (ddt, *J* 17.0, 10.2, 6.6, 1H, *H*-9), 6.00 – 5.96 (m, 2H, *H*-10), 3.74 (s, 3H, -OCH_3), 3.40 – 3.37 (m, 0.5H, *H*-2'), 2.33 (dq, *J* 11.9, 5.9, 1H, *H*-6), 2.26 – 1.20 (m, 10H, *H*-3,4,5,7 & 8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.2 (*C*-1'), 174.8 (*C*-1), 138.2 (*C*-9), 114.9 (*C*-10), 97.6 (*C*-2), 57.9 (*C*-2'), 51.9 (*C*H_3), 37.9 (*C*-6), 34.2 (*C*H_2), 31.2 (*C*H_2), 27.0 (*C*H_2), 24.1 (*C*H_2), 20.0 (*C*H_2); **HRMS** (ESI^+) 211.1332 $[M + H]^+$, 233.1150 $[M + Na]^+$ ($C_{12}H_{19}O_3$ requires 211.1329, $C_{12}H_{18}NaO_3$ requires 233.1148).

120b – (±)-Ethyl 3-(but-3-en-1-yl)-2-oxocyclohexane-1-carboxylate

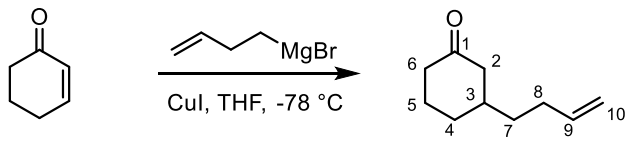


120b

A solution of ethyl 2-oxocyclohexane-1-carboxylate (1.00 g, 5.88 mmol) in THF (2.0 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.47 g, 11.75 mmol) in THF (20 mL) at 0 °C. After 15 min, a solution of *n*-butyllithium (2.5 M in hexanes, 3.76 mL, 9.40 mmol) was added dropwise and stirred at 0 °C for 1 h. A solution of 1-bromobut-4-ene (0.59 mL, 0.79 g, 5.88 mmol) in THF (1.0 mL) was added dropwise and stirred at 0 °C

for 2 h before warming to room temperature. After 18 h at room temperature, the reaction was quenched with water (10 mL) and the solvent removed under reduced pressure. Saturated aqueous ammonium chloride solution (10 mL) was added and the product extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The product was purified by column chromatography (5% ethyl acetate/petroleum ether) to give a 1:1 mixture of the keto/enol tautomers of the product **120b** (0.92 g, 70%) as a yellow oil; **IR** υ_{max}/cm^{-1} 2927, 2857, 1744, 1714, 1642, 1617; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.42 (s, 0.5H, O*H*), 5.78 (m, 1H, *H*-9), 5.08 – 4.90 (m, 2H, *H*-10), 4.19 (q, *J* 7.2, 1H, C*H*$_2$CH$_3$), 3.37 (m, 0.5H, *H*-2'), 2.33 (m, 1H, *H*-6), 2.29 – 1.34 (m, 10H, *H*-3,4,5,7 & 8), 1.29 (t, *J* 7.2, 2H, CH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.3 (*C*-1'), 174.6 (*C*-1), 138.2 (*C*-9), 114.9 (*C*-10), 97.7 (*C*-2), 60.4 (C*H*$_2$CH$_3$), 57.9 (*C*-2'), 37.9 (*C*-6), 34.2 (C*H*$_2$), 31.2 (C*H*$_2$), 27.1 (C*H*$_2$), 24.1 (C*H*$_2$), 20.0 (C*H*$_2$), 14.2 (CH$_2$C*H*$_3$); **HRMS** (ESI$^+$) 225.1496 $[M + H]^+$, ($C_{13}H_{21}O_3$ requires 225.1485).

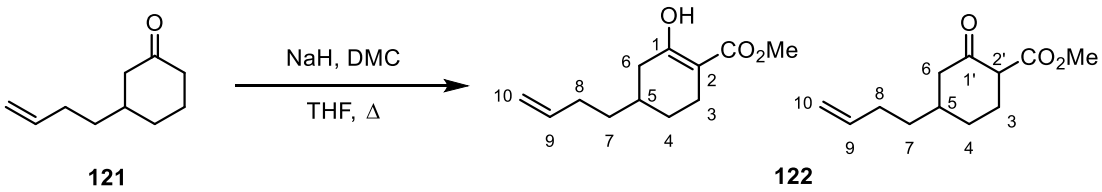
121 – (±)-3-(But-3-en-1-yl)cyclohexan-1-one



121

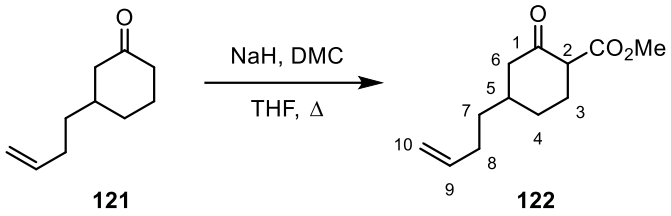
Copper iodide (25 mg, 0.25 mmol) was added to a solution of freshly prepared butenylmagnesium bromide (10.0 mmol) in THF (25 mL) at 0 °C. After 40 min a solution of cyclohexanone (0.48 mL, 0.48 g, 5.00 mmol) in THF (20 mL) was added dropwise over 15 min and then the reaction mixture slowly warmed to room temperature. After 5 h, the reaction mixture was poured into saturated aqueous ammonium chloride solution (50 mL) and the organics extracted with DCM (3 × 75 mL) and the organic layers washed with brine, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography (5% ethyl acetate/petroleum ether) to give the pure product **121**; (0.78 g, quant.) as a colourless oil; **IR** υ_{max}/cm^{-1} 2925, 2851, 1712, 1640; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* 16.9, 10.2, 6.7, 1H, *H*-9), 5.00 – 4.95 (m, 2H, *H*-10), 2.42 (m, 1H, *H*-2), 2.34 (m, 1H, *H*-6), 2.25 (m, 1H, *H*-6), 2.10 – 1.96 (m, 4H, *H*-2,5 & 8), 1.89 (m, 1H, *H*-4), 1.78 (m, 1H, *H*-3), 1.64 (m, 1H, *H*-5), 1.42 – 1.36 (m, 3H, *H*-4 & 7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.8 (*C*-1), 138.2 (*C*-9), 114.8 (*C*-10), 48.0 (*C*-2), 41.5 (*C*-6), 38.4 (*C*-3), 35.7 (*C*-7), 31.2 (*C*-4), 30.8 (*C*-8), 25.2 (*C*-5); **HRMS** (ESI$^+$) 175.1099 $[M + Na]^+$, 327.2294 $[2M + Na]^+$ ($C_{10}H_{16}NaO$ requires 175.1093, $C_{20}H_{32}NaO_2$ requires 327.2300).

122 – (±)-5-(But-3-en-1-yl)-1-oxocyclohexane-2-carboxylate



Sodium hydride (60% dispersion in mineral oil, 0.63 g, 15.9 mmol) and dimethyl carbonate (1.07 mL, 1.15 g, 12.8 mmol) were dissolved in THF (10.0 mL) and heated at reflux. A solution of **121** (0.78 g, 5.12 mmol) in THF (5.0 mL) was added dropwise over 20 min and then stirred at reflux for a further 6.5 h. The reaction was cooled to 0 °C and quenched with acetic acid (3.0 M, 1 mL), poured into brine (10 mL), and extracted with DCM (3 × 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give a 1:1 mixture of the keto/enol tautomers of **122** as a colourless oil (0.91 g, 84%); **IR** υ_{max}/cm^{-1} 3675, 2924, 1711, 1659, 1619; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.10 (s, 0.5H, O*H*), 5.80 (ddt, *J* 16.9, 10.0, 6.6, 1H, *H*-9), 5.02 – 4.98 (m, 2H, *H*-10), 3.74 (s, 3H, -OC*H*$_3$), 3.35 (m, 0.5H, *H*-2') 2.36 – 2.32 (m, 2H, *H*-4 & *H*-6), 2.12 – 2.06 (m, 3H, *H*-8 & *H*-4), 1.95 (m, 1H, *H*-6), 1.78 (dddd, *J* 13.1, 5.2, 3.2, 1.7, 1H, *H*-3), 1.67 (dtd, *J* 9.2, 6.2, 3.4, 1H, *H*-5), 1.42 – 1.38 (m, 2H, *H*-7), 1.18 (dtd, *J* 13.1, 10.8, 5.5, 1H, *H*-3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.5 (*C*-1'), 171.5 (*C*-1), 138.5 (*C*-9), 114.6 (*C*-10), 97.4 (*C*-2), 57.1 (*C*-2'), 51.3 (-O*C*H$_3$), 35.3 (*C*-6), 35.0 (*C*-7), 32.6 (*C*-5), 31.0 (*C*-8), 28.5 (*C*-3), 21.9 (*C*-4); **HRMS** (ESI^+) 211.1332 $[M + H]^+$, 233.1159 $[M + Na]^+$ ($C_{12}H_{19}O_3$ requires 211.1329, $C_{12}H_{18}NaO_3$ requires 233.1148).

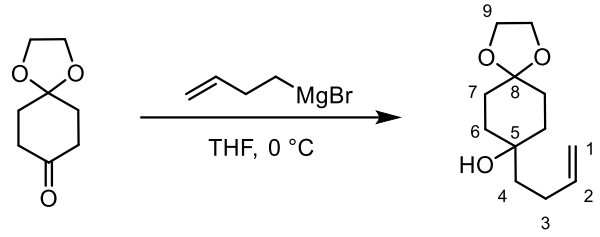
122 – (±)-Methyl 5-(but-3-en-1-yl)-1-oxocyclohexane-2-carboxylate



Dimethyl carbonate (1.15 g, 12.8 mmol) and sodium hydride (60% dispersion in mineral oil, 0.63 g, 15.9 mmol) added to THF (10 mL) and heated at reflux. After 15 min a solution of **121** (0.78 g, 5.10 mmol) in THF (5 mL) was added dropwise. After 5 h at reflux, the reaction mixture was cooled to room temperature and cautiously quenched with acetic acid (3.0 M, 2 mL) and then water (10 mL). The solution was poured into brine (10 mL) then extracted with DCM (3 × 10 mL), and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (5% ethyl acetate/petroleum ether) to give a 1:1 mixture of keto/enol

tautomers **122** (0.90 g, 84%) as a colourless oil (data given for the keto tautomer); **IR** υ_{max}/cm^{-1} 3676, 2953, 2925, 1752, 1716, 1664, 1623, 1442, 1218; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.10 (s, 0.5H, OH), 5.80 (ddt, *J* 16.9, 10.0, 6.6, 1H, *H*-9), 5.05 – 4.96 (m, 2H, *H*-10), 3.74 (s, 3H, OC*H*$_3$), 3.35 (m, 0.5H, *H*-2'), 2.39 – 2.29 (m, 2H, *H*-4 & *H*-6), 2.15 – 2.07 (m, 3H, *H*-8 & *H*-4), 1.95 (m, 1H, *H*-6), 1.78 (dddd, *J* 13.1, 5.2, 3.2, 1.7, 1H, *H*-3), 1.67 (dtd, *J* 9.2, 6.2, 3.4, 1H, *H*-5), 1.45 – 1.35 (m, 2H, *H*-7), 1.18 (dtd, *J* 13.1, 10.8, 5.5, 1H, *H*-3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.5 (*C*-1), 138.5 (*C*-9), 114.6 (*C*-10), 57.1 (*C*-2), 51.3 (-O*C*H$_3$), 35.3 (*C*-6), 35.0 (*C*-7), 32.6 (*C*-5), 31.0 (*C*-8), 28.5 (*C*-3), 21.9 (*C*-4); **HRMS** (ESI^+) 233.1147 $[M + Na]^+$ ($C_{12}H_{18}NaO_3$ requires 233.1148).

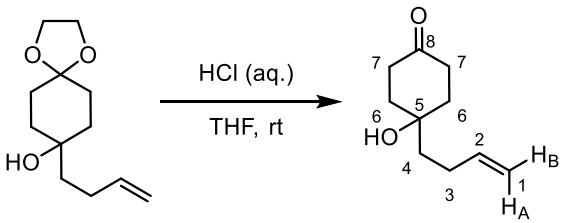
S5 – (±)-8-(But-3-en-1-yl)-1,4-dioxaspiro[4.5]decan-8-ol



S5

A freshly prepared solution of butenylmagnesiumbromide (1.2 equiv.) in THF (5 mL) was added dropwise to a solution of 1,4-cyclohexanedione monoethylene acetal (0.81 g, 5.2 mmol) in dry THF (7.5 mL) at 0 °C. The resulting solution was allowed to warm slowly to room temperature overnight. After 18 h, the reaction was quenched with saturated ammonium chloride solution (5 mL), extracted with diethyl ether (3 × 10 mL) and the combined organic extracts dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give an orange oil. The crude product was purified by column chromatography (20-50% ethyl acetate/petroleum ether) to give the pure product **S5** (0.22 g, 20%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3478, 2930, 1712, 1640; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 (ddt, *J* 16.8, 10.2, 6.6, 1H, *H*-2), 5.08 – 4.91 (m, 2H, *H*-1), 4.00 – 3.87 (m, 4H, 2 × *H*-9), 2.21 – 2.10 (m, 2H, *H*-3), 1.94 – 1.80 (m, 2H, C*H*$_2$), 1.69 – 1.50 (m, 8H, 4 × C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.0 (*C*-2), 114.5 (*C*-1), 108.8 (*C*-8), 70.5 (*C*-5), 64.2 (*C*-9), 41.5 (*C*-4), 34.7 (*C*-6/7), 30.5 (*C*-6/7), 27.8 (*C*-3); **HRMS** (ESI^+) 235.1308 $[M + Na]^+$ ($C_{12}H_{20}NaO_3$ requires 235.1305).

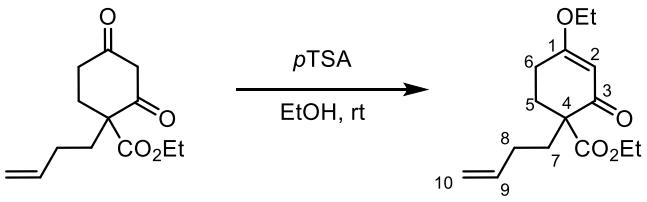
123 – (±)-5-(But-3-en-1-yl)-1-hydroxycyclohexan-8-one



S5 **123**

S5 (0.20 g, 0.94 mmol) was stirred in hydrochloric acid (2.0 M, 10 mL) and THF (10 mL) at room temperature for 18 h. After removal of the solvent under reduced pressure, the remaining aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give **123** (0.12 g, 78%) as a yellow oil; **IR** υ_{max}/cm^{-1} 3434 3073, 2933, 2855, 1704, 1640; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.87 (ddt, *J* 17.1, 10.2, 6.6, 1H, *H*-2), 5.08 (dq, *J* 17.1, 1.5, 1H, *H*-1_A), 5.00 (dq, *J* 10.2, 1.5, 1H, *H*-1_B), 2.73 – 2.69 (m, 2H, *H*-6/7), 2.25 – 2.20 (m, 4H, *H*-3 & *H*-6/7), 1.98 (ddt, *J* 14.6, 6.4, 3.2, 2H, *H*-6/7), 1.80 (td, *J* 13.6, 5.2, 2H, *H*-6/7), 1.69 – 1.65 (m, 2H, *H*-4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.0 (*C*-8), 138.5 (*C*-2), 115.1 (*C*-1), 70.3 (*C*-5), 41.4 (*C*-4), 36.9 (*C*-6), 36.9 (*C*-7), 28.0 (*C*-3); **HRMS** (ESI^+) 151.1112 $[M + H - H_2O]^+$, 191.1045 $[M + Na]^+$ ($C_{10}H_{15}O$ requires 151.1117, $C_{10}H_{16}NaO_2$ requires 191.1043).

S6– (±)-Ethyl 4-(but-3-en-1-yl)-1-ethoxy-3-oxocyclohex-2-ene-4-carboxylate

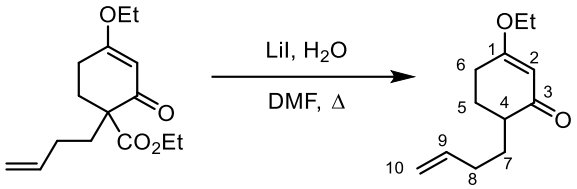


128 **S6**

128 (1.0 g, 4.2 mmol) and *p*TSA (0.13 g, 0.67 mmol) were stirred in ethanol (10 mL) at room temperature for 16 h. The reaction was quenched with saturated sodium hydrogen carbonate solution (5 mL), extracted with TBME (3 × 10 mL) and the combined organics dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography (0-20% ethyl acetate/petroleum ether) to give **S6** (0.75 g, 67%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2932, 1980, 1726, 1663, 1608, 1187; **^{1}H NMR** (500 MHz, $CDCl_3$) 5.81 (tdd, *J* 16.5, 8.2, 4.9, 1H, *H*-9), 5.35 (s, 1H, *H*-2), 5.03 (d, *J* 16.5, 1H, *H*-10), 4.95 (d, *J* 8.2, 1H, *H*-10), 4.17 (q, *J* 7.1, 2H, -OC*H*$_2$CH$_3$), 3.90 (q, *J* 7.1, 2H, -OC*H*$_2$CH$_3$), 2.62 (ddd, *J* 17.9, 9.5, 5.1, 1H, *H*-6) 2.45 (dt, *J* 14.0, 5.1, 1H, *H*-5), 2.36 (dt, *J* 17.9, 5.1, 1H, *H*-6), 2.12 – 1.99 (m, 3H, *H*-8 & *H*-7), 1.93 (ddd, *J* 14.0, 9.5, 5.1, 1H, *H*-5), 1.83 (m, 1H, *H*-7), 1.36 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$), 1.24 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (126

MHz, $CDCl_3$) 195.4 (*C*-3), 176.2 (*C*-1), 171.4 (*C*=O), 137.8 (*C*-9), 114.5 (*C*-10), 101.7 (*C*-2), 64.1 (-O*C*H_2CH$_3$), 60.9 (-O*C*H_2CH$_3$), 55.4 (*C*-4), 32.8 (*C*-7), 28.6 (*C*-8), 28.1 (*C*-5), 26.2 (*C*-6), 13.8 (-OCH$_2$*C*H$_3$), 13.8 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 267.1589 [M+H]$^+$ ($C_{15}H_{23}O_4$ requires 267.1591).

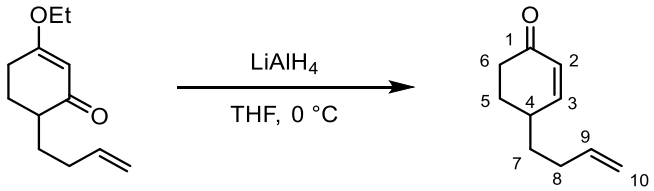
125 – (±)-4-(But-3-en-1-yl)-1-ethoxycyclohex-2-en-3-one



S6 **125**

S6 (3.48 g, 13.1 mmol) and lithium iodide (4.37 g, 32.7 mmol) were heated at reflux in DMF (35 mL) and H_2O (1 drop). After 8 h the reaction mixture was cooled to room temperature and diluted with diethyl ether (30 mL) and hydrochloric acid (2.0 M, 30 mL) added. The aqueous layer was extracted with diethyl ether (3 × 50 mL) and the organics washed with water (3 × 50 mL) and then dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (0-10% ethyl acetate/petroleum ether) to give **125** (1.0 g, 39%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2980 (w), 2930 (w), 1728 (w), 1655, 1608 (s), 1379, 1190; **^{1}H NMR** (500 MHz, $CDCl_3$) 5.82 (ddt, *J* 16.9, 10.2, 6.6, 1H, *H*-9), 5.31 (s, 1H, *H*-2), 4.86 – 5.12 (m, 2H, *H*-10), 3.89 (q, *J* 7.0, 2H, -OC*H*$_2$CH$_3$), 2.42 (dd, *J* 6.9, 5.5, 2H, *H*-6), 2.14 – 2.25 (m, 2H, *H*-4 & *H*-8), 2.04 – 2.13 (m, 2H, *H*-5 & *H*-8), 1.99 (m, 1H, *H*-7), 1.73 (m, 1H, *H*-5), 1.44 (dtd, *J* 13.8, 9.0, 5.5, 1H, *H*-7), 1.36 (t, *J* 7.0, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) 201.2 (*C*-3), 176.4 (*C*-1), 138.1 (*C*-9), 114.5 (*C*-10), 102.0 (*C*-2), 63.9 (-O*C*H_2CH$_3$), 44.2 (*C*-4), 30.9 (*C*-8), 28.4 (*C*-7), 27.7 (*C*-6), 25.9 (*C*-5), 13.9 (-OCH$_2$C*H*$_3$); **HRMS** (ESI$^+$) 195.1381 [M+H]$^+$ ($C_{12}H_{19}O_2$ requires 195.1380).

126 – (±)-4-(But-3-en-1-yl)cyclohex-2-en-1-one

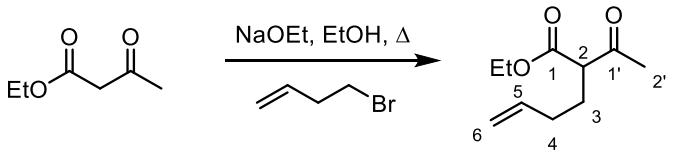


125 **126**

A solution of lithium aluminium hydride in THF (1.0 M, 5.2 mL) was added to a solution of **125** (1.0 g, 5.15 mmol) in THF (10 mL) at 0 °C. After addition was complete the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched by the slow addition of water at 0 °C and stirred for 30 min before adding hydrochloric acid (1.0 M, 10 mL) and extracting with diethyl ether (3 × 20 mL). The combined organic layers were dried over

magnesium sulfate, filtered, and the solvent removed under reduced pressure to give the crude product as a colourless oil. The product was purified by column chromatography (5-10% ethyl acetate/petroleum ether to give **126** (0.61 g, 79%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2924 (w), 1734 (w), 1678 (s) 1453, 1113; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87 (ddd, *J* 10.2, 2.8, 0.8, 1H, *H*-3), 5.99 (ddd, *J* 10.2, 2.8, 1.4, 1H, *H*-2), 5.83 (ddt, *J* 17.0, 10.2, 6.6, 1H, *H*-9), 5.08 (dq, *J* 17.0, 1.6, 1H, *H*-10), 5.03 (dq, *J* 10.2, 1.6, 1H, *H*-10), 2.51 (dddd, *J* 16.9, 5.2, 4.3, 0.8, 1H, *H*-6), 2.45 (m, 1H, *H*-4), 2.37 (ddd, *J* 16.9, 12.3, 4.9, 1H, *H*-6), 2.23 – 2.10 (m, 3H, *H*-5 & *H*-8), 1.77 – 1.47 (m, 3H, *H*-5 & *H*-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.9 (*C*-1), 154.8 (*C*-3), 137.8 (*C*-9), 129.1 (*C*-3), 115.4 (*C*-10), 36.9 (*C*-6), 35.4 (*C*-4), 33.7 (*C*-7), 31.0 (*C*-8), 28.5 (*C*-5); **HRMS** (ESI^+) 151.1112 $[M+H]^+$ ($C_{10}H_{15}O$ requires 151.1117).

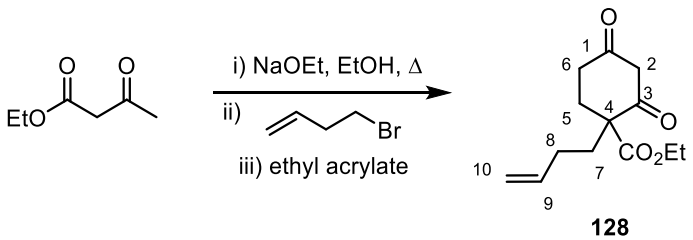
127 – (±)-Ethyl 2-acetylhex-5-enoate



127

Ethyl acetoacetate (0.98 mL, 1.0 g, 7.68 mmol) was added dropwise to a solution of sodium ethoxide (2.37 mL, 3.0 M in ethanol) and stirred at room temperature for 1 h. 1-Bromobut-4-ene (0.74 mL, 0.99 g, 7.31 mmol) was added and the solution heated at reflux for 16 h. The reaction was cooled to room temperature and ethyl acetate (20 mL) added, then washed with hydrochloric acid (20 mL, 0.5 M) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give the product **127** (0.95 g, 67%) as a yellow oil; **^{1}H-NMR** (400 MHz, $CDCl_3$) 5.76 (ddt, *J* 17.0, 10.2, 6.6, 1H, *H*-5), 5.09 – 4.99 (m, 2H, *H*-6), 4.20 (q, *J* 7.1, 2H, -OC*H*$_2$CH$_3$), 3.45 (t, *J* 7.2, 1H, *H*-2), 2.23 (s, 3H, *H*-2'), 2.12 – 2.05 (m, 2H, *H*-4), 1.99 – 1.92 (m, 2H, *H*-3), 1.28 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **HRMS** (ESI^+) 185.1176 $[M+H]^+$ ($C_{10}H_{17}O_3$ requires 185.1172). Data in accordance with literature.[210]

128 – (±)-Ethyl 4-(but-3-en-1-yl)-1,3-dioxocyclohexane-4-carboxylate

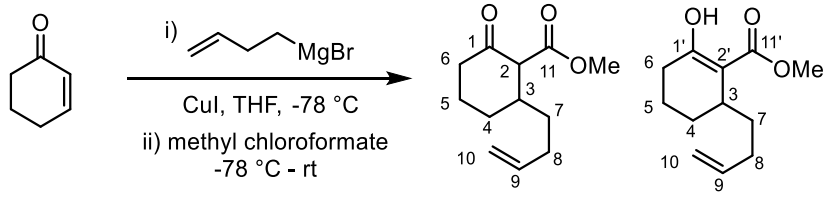


128

Ethyl acetoacetate (4.9 mL, 5.0 g, 38.4 mmol) was added dropwise to a solution of sodium ethoxide (14.1 mL, 3.0 M in ethanol) at room temperature. After 1 h, 1-bromobut-4-ene was

added and the solution was heated at reflux for 5 h. A further portion of sodium ethoxide (14.1 mL, 3.0 M in ethanol) was added and stirred for 15 min before ethyl acrylate (4.4 mL, 4.0 g, 40.3 mmol) was added and the solution left at reflux for 16 h. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The resulting residue was re-dissolved in water (20 mL) and extracted with TBME (3 × 20 mL). The aqueous layer was acidified with hydrochloric acid (2 M) and re-extracted with TBME (3 × 20 mL). The combined organics were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (0-10% ethyl acetate/petroleum ether) to give the product **128** (5.17 g, 57%) as a colourless oil, found to be a 1:0.9 mixture of keto/enol tautomers as a solution in $CDCl_3$. Data given for the major ketone tautomer; **IR** υ_{max}/cm^{-1} 2979 (br), 1726, 1596, 1190; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.72 (m, 1H, *H*-9), 4.99 – 4.92 (m, 2H, *H*-10), 4.18 (q, *J* 7.1, 2H, -OC*H*$_2$CH$_3$), 3.60 (dd, *J* 17.0, 0.7, 1H, *H*-2), 3.33 (dd, *J* 17.0, 1.6, 1H, *H*-2), 2.58 – 2.50 (m, 2H, *H*-6), 2.45 (ddd, *J* 14.3, 5.8, 3.6, 1H, *H*-5), 2.09 (m, 1H, *H*-7), 2.05 – 1.94 (m, 2H, *H*-7 & *H*-8), 1.78 (m, 1H, *H*-8), 1.66 (ddd, *J* 14.3, 12.0, 5.9, 1H, *H*-5), 1.22 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.1 (*C*-1), 199.6 (*C*-3), 170.8 (*C*=O), 137.3 (*C*-9), 115.4 (*C*-10), 62.1 (-O*C*H$_2$CH$_3$), 59.3 (*C*-4), 57.5 (*C*-2), 37.5 (*C*-6), 33.2 (*C*-8), 28.6 (*C*-7), 27.3 (*C*-5), 14.1 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 239.1280 $[M+H]^+$ ($C_{13}H_{19}O_4$ requires 239.1278).

132a – (±)-Methyl-3-(but-3-en-1-yl)-1-oxocyclohexane-2-carboxylate

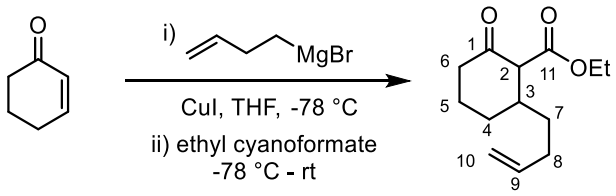


132a

Magnesium (0.19 g, 7.8 mmol) was heated for 15 min under vacuum with a single crystal of iodine. THF (5.0 mL) was added before a solution of 1-bromobut-4-ene (0.63 mL, 0.84 g, 6.24 mmol) in THF (2.5 mL) was added dropwise causing an exothermic reaction. After 30 min, the Grignard solution was added dropwise to a solution of copper iodide (1.1 g, 5.72 mmol) in THF (12.5 mL) at -78 °C. The suspension was stirred at -78 °C for 1 h before adding a solution of cyclohexenone (0.50 mL, 0.50 g, 5.2 mmol) in THF (5.0 mL) at -78 °C via cannula causing the solution to turn bright yellow. After 1 h, the solution was warmed to 0 °C for ca. 20 min and then cooled to -78 °C. Methyl chloroformate (0.44 mL, 0.54 g, 5.72 mmol) was added dropwise before allowing the solution to slowly warm to room temperature. After 18 h, the solution was diluted with DCM (40 mL) and then quenched with saturated ammonium chloride

solution (30 mL). The product was extracted with DCM (3 × 75 mL) and the organic layers washed with brine, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography (5% ethyl acetate/petroleum ether) to give a 1:1 mixture of keto-enol tautomers of **132a** (0.15 g, 14%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2927, 2855, 1759, 1718, 1651, 1266; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.34 (s, 1H, O*H*), 5.82 (m, 2H, *H*-9), 5.05 – 4.98 (m, 4H, *H*-10), 3.82 (s, 3H, C*H*$_3$), 3.78 (s, 3H, C*H*$_3$), 2.55 (m, 1H, *H*-3), 2.27 (m, 1H, *H*-3), 3.16 (dd, *J* 10.9, 1.1, 1H, *H*-2) 2.38 – 1.16 (m, 20H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.9 (*C*-1), 173.2 (*C*-11), 172.7 (*C*-1'), 154.1 (*C*-11'), 138.9 (*C*-9), 138.6 (*C*-9), 114.6 (*C*-10), 114.2 (*C*-10), 102.5 (*C*-2'), 63.6 (*C*-2), 54.9 (-O*C*H$_3$), 51.3 (-O*C*H$_3$), 35.1 (*C*H$_2$), 33.8 (*C*-3), 33.4 (*C*H$_2$), 32.0 (*C*H$_2$), 31.1 (*C*H$_2$), 31.0 (C-3), 29.1 (*C*H$_2$), 28.0 (*C*H$_2$), 26.5 (*C*H$_2$), 25.2 (*C*H$_2$), 21.4 (*C*H$_2$), 17.0 (*C*H$_2$); **HRMS** (ESI$^+$) 211.1333 [M + H]$^+$, 233.1160 [M + Na]$^+$ ($C_{12}H_{19}O_3$ requires 211.1329, $C_{12}H_{18}NaO_3$ requires 233.1148).

132b – (±)-Ethyl 2-(but-3-en-1-yl)-6-oxocyclohexane-1-carboxylate

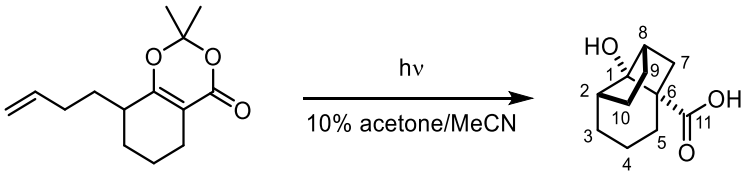


132b

1-Bromobut-4-ene (0.27 g, 2.0 mmol, 0.2 mL) was dissolved in THF (1 mL) and added dropwise to a suspension of magnesium (58 mg, 2.4 mmol) in THF (1 mL) at room temperature. After 40 min, the solution was diluted with further THF (20 mL) and cooled to 0 °C. Copper iodide (5 mg, 0.05 mmol) was added, and the reaction stirred at 0 °C for 1 h. A solution of cyclohex-2-en-1-one (96 mg, 1.0 mmol) in THF (1 mL) was added dropwise at 0 °C. After stirring for 3 h at 0 °C a solution of ethyl cyanoformate (0.11 g, 1.1 mmol, 0.11 mL) in THF (1.0 mL) was added dropwise and stirred at 0 °C for a further 1 h. The reaction was quenched with saturated ammonium chloride solution (6 mL), extracted with DCM (3 × 20 mL) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give **132b** (0.15 g, 69%) as a 3:1 mixture of the keto:enol tautomers (NMR data given for the major keto-tautomer); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.70 (m, 1H, *H*-9), 4.99 – 4.86 (m, 2H, *H*-10), 4.21 – 4.16 (m, 2H, -OC*H*$_2$CH$_3$), 3.05 (dd, *J* 10.8, 1.1, 1H, *H*-2), 2.42 (m, 1H, *H*-6), 2.24 – 2.18 (m, 2H, *H*-3 & *H*-6), 2.08 (m, 1H, *H*-8), 2.05 – 1.93 (m, 3H, *H*-8, *H*-4 & *H*-5), 1.63 (m, 1H, *H*-5), 1.39 – 1.31 (m, 3H, H-7, *H*-4), 1.21 (t, *J* 7.2, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.1 (*C*-1), 169.8 (*C*-11), 137.9 (*C*-9), 115.0 (*C*-10), 63.7 (*C*-2), 60.9 (-O*C*H$_2$CH$_3$), 41.1 (*C*-6), 40.5 (*C*-3), 34.0 (*C*-7), 30.7 (*C*-8), 28.7 (*C*-4), 24.6 (*C*-5), 14.2

(-OCH_2CH_3); **IR** υ_{max}/cm^{-1} 2982, 2936, 2857, 1742, 1713, 1641; **HRMS** (ESI^+) 225.1484 $[M + H]^+$ 247.1303 $[M + Na]^+$ ($C_{13}H_{21}O_3$ requires 225.1485, $C_{13}H_{20}NaO_3$ requires 247.1305).

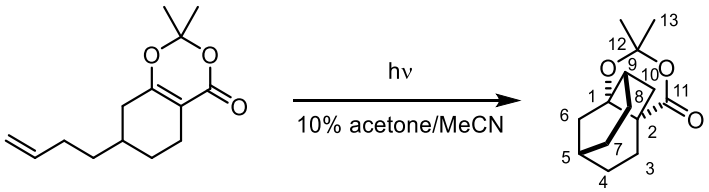
135 – (±)-(1R,2S,6S, 8S)-1-hydroxyoctahydrocyclobuta[cd]indene-6(1H)-carboxylic acid



119a **135**

A solution of **119a** (0.12 g, 0.51 mmol) was dissolved in 10% acetone/acetonitrile (150 mL) and irradiated with a 125 W medium pressure UV lamp. After 5 h the solvent was removed under reduced pressure and the product purified by column chromatography (5% ethyl acetate/petroleum ether) to give **135** (62 mg, 62%) as a colourless solid; **IR** υ_{max}/cm^{-1} 3446 (br), 2954 (w), 2256 (w), 1717 (s), 1424, 1371; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.70 (m, 1H, *H*-8), 2.27 (ddt, *J* 11.0, 7.0, 3.0, 1H, *H*-2), 2.01 (dd, *J* 12.5, 9.5, 1H, *H*-7), 1.91 – 1.56 (m, 10H, *H*-3,4,5,9 & 10), 1.52 (dd, *J* 12.5, 8.0 1H, *H*-7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 183.6 (*C*-11), 79.7 (*C*-1), 50.0 (*C*-6), 46.1 (*C*-8), 44.5 (*C*-2), 29.3 (*C*-9), 28.9 (*C*-10), 27.4 (*C*-5), 23.9 (*C*-3), 22.6 (*C*-7), 16.0 (*C*-4); **HRMS** (ESI^-) 195.1025 $[M - H]^-$ ($C_{11}H_{15}O_3$ requires 195.1027).

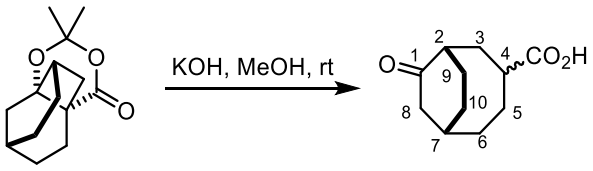
136 – (±)-(4a*S*,5a*S*,8*R*,9a*R*)-2,2-dimethylhexahydro-4H-4a,8-ethanobenzo[1,4]cyclobuta[1,2d][1,3]-dioxin-4-one*



119b **136**

119b (0.27 g, 1.14 mmol) was dissolved in 10% acetone/acetonitrile (150 mL) and irradiated with a 125 W medium pressure mercury lamp. After 5.5 h, the solvent was removed under reduced pressure and the product purified by column chromatography (20-50% ethyl acetate/petroleum ether) to give **136** (0.15 g, 55%) as a colourless solid; **IR** υ_{max}/cm^{-1} 2939, 2865, 1732, 1294; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.48 – 2.41 (m, 2H, H-9 & H-10), 2.38 (m, 1H, H-5), 2.37 (m, 1H, H-10), 2.19 – 2.09 (m, 2H, CH_2), 2.04 – 1.85 (m, 4H, 2 × CH_2), 1.81 – 1.65 (m, 2H, CH_2), 1.64 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.62 – 1.47 (m, 2H, CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) 175.6 (*C*-11), 105.4 (*C*-12), 75.3 (*C*-1), 38.9 (*C*-2), 36.9 (*C*-9), 29.8 (*C*-13), 29.4 (*C*-6), 29.0 (*C*-13), 28.9 (CH_2), 28.7 (*C*-10), 28.3 (CH_2), 27.9 (CH_2), 24.5 (*C*-5), 22.9 (CH_2); **HRMS** (ESI^+) 259.1299 $[M + Na]^+$ ($C_{14}H_{20}NaO_3$ requires 259.1305).

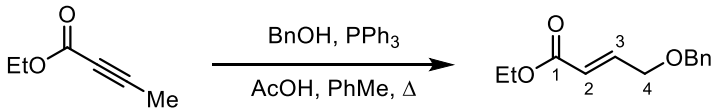
138 – (±)-1-(2*S*,7*R*)Oxobicyclo[4.2.2]decane-4-carboxylic acid



136 **138**

136 (0.15 g, 0.63 mmol) was added to a solution of potassium hydroxide in methanol (2.0 M, 10 mL) at room temperature. After 16 h the mixture was diluted with water (5 mL) and acidified with hydrochloric acid (3 M). The aqueous solution was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give the product **138** (41 mg, 33%) as an orange oil; **IR** υ_{max}/cm^{-1} 3055, 2937, 2916, 2643, 1727, 1699; **^{1}H NMR** (500 MHz, $CDCl_3$) 2.70 (ddd, *J* 12.9, 8.9, 4.6, 1H, *H*-4), 2.63 (m, 1H, *H*-2), 2.58 – 2.50 (m, 2H, *H*-7 & *H*-8), 2.32 (d, *J* 16.7, 1H, *H*-8), 2.24 – 2.02 (m, 5H, *H*-3,5,9,10), 1.90 – 1.82 (m, 2H, H-6 & *H*-9), 1.74 – 1.62 (m, 2H, *H*-6 & *H*-10), 1.29 (dddd, *J* 13.5, 12.2, 9.0, 4.5, 1H, *H*-5); **^{13}C NMR** (126 MHz, $CDCl_3$) 218.9 (*C*-1), 181.9 (*C*=O), 44.7 (*C*-2), 42.6 (*C*-8), 42.2 (*C*-4), 38.1 (*C*-3), 36.9 (*C*-6), 29.2 (*C*-7), 26.7 (*C*-5), 24.9 (*C*-10), 22.6 (*C*-9); **HRMS** (ESI^+) 219.0981 $[M + Na]^+$ ($C_{11}H_{16}NaO_3$ requires 219.0992).

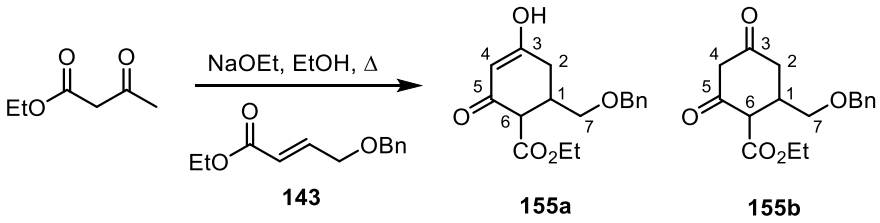
143 – Ethyl (*E*)-4-(benzyloxy)but-2-enoate



143

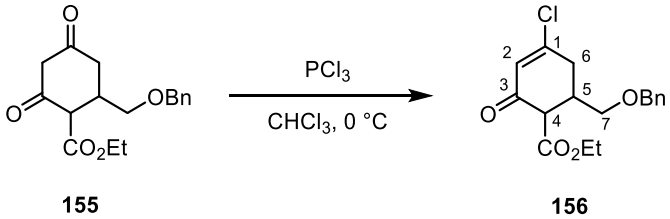
Ethyl but-2-ynoate (5.00 g, 44.6 mmol, 5.20 mL), phenylmethanol (4.80 g, 44.6 mmol, 4.60 mL), triphenyl phosphine (0.58 g, 2.23 mmol) and acetic acid (0.54 g, 8.90 mmol, 0.50 mL) were dissolved in toluene (50 mL) and heated to 90 °C. After 24 h, the reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The product was purified by column chromatography (5% diethyl ether/petroleum ether) to give **143** (7.38 g, 75%) as a colourless oil as well as the *cis*-isomer (0.56 g, 5%); **IR** υ_{max}/cm^{-1} 2990, 2853, 1716, 1659; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.18 (m, 5H, C*H* arom.), 6.90 (dt, *J* 15.7, 4.3, 1H, *H*-3), 6.05 (dt, *J* 15.7, 2.0, 1H, *H*-2), 4.48 (s, 2H, PhCH_2), 4.18 – 4.05 (m, 4H, -OC$H_2$$CH_3$ & *H*-4), 1.21 (t, *J* 7.1, 3H, -OCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (*C*-1), 144.2 (*C*-3), 137.8 (*C* arom.), 128.5 (*C*H arom.), 127.8 (*C*H arom.), 127.6 (*C*H arom.), 121.5 (*C*-2), 72.8 (Ph*C*H_2), 68.7 (*C*-4), 60.4 (-O*C*H_2CH_3), 14.3 (-OCH_2*C*H_3); **HRMS** (ESI^+) 243.1000 $[M + Na]^+$ ($C_{13}H_{16}NaO_3$ requires 243.0992). Data in accordance with literature.[211]

155 – (±)-Ethyl 1-((benzyloxy)methyl)-3,5-dioxocyclohexane-6-carboxylate



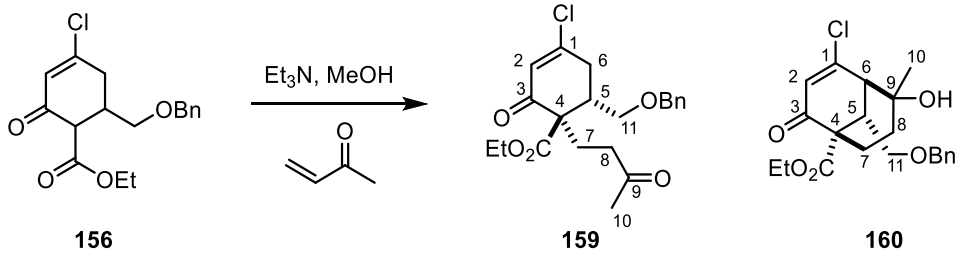
Sodium metal (1.41 g, 61.3 mmol) was added to dry ethanol (90 mL) and stirred at room temperature for 2 h. Ethyl acetoacetate (7.12 mL, 55.9 mmol) and **143** (12.9 g, 58.7 mmol) were added dropwise and the mixture heated at reflux. After 48 h, the reaction was cooled to room temperature and the solvent removed under reduced pressure. The resulting red residue was dissolved in water (100 mL) and washed with diethyl ether (100 mL). The aqueous layer was acidified with hydrochloric acid (3.0 M) and then extracted with ethyl acetate (3 × 10 mL) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by recrystallisation from diethyl ether to give **155** (12.00 g, 70%) as a colourless solid (found to be a 1:0.75 mixture of enol/keto tautomers in $CDCl_3$ labelled (a) and (b) respectively); **m.p.** (diethyl ether) 82 – 83 °C; **IR** υ_{max}/cm^{-1} 2926, 2857, 1734, 1650, 1606, 1211; **^{1}H NMR** (500 MHz, $CDCl_3$) 9.66 (s, 1H, O*H*), 7.45 – 7.21 (m, 8H, C*H* arom.), 7.22 (d, *J* 7.0, 2H, C*H* arom.), 5.52 (s, 1H, *H*-4a), 4.51 (d, *J* 12.0, 1H, PhC*H*$_2$a), 4.48 (d, *J* 12.0, 1H, PhC*H*$_2$a), 4.43 (d, *J* 12.0, 1H, PhC*H*$_2$b), 4.40 (d, *J* 12.0, 1H, PhC*H*$_2$b), 4.30 – 4.11 (m, 4H, -OC*H*$_2$CH$_3$), 3.63 (dt, *J* 4.3, 1.4, 1H, *H*-6b), 3.57 – 3.47 (m, 2H, *H*-4b & *H*-7b), 3.46 – 3.42 (m, 3H, *H*-7a & *H*-6a), 3.36 (dt, *J* 18.0, 1.7, 1H, *H*-4b), 2.91 – 2.71 (m, 3H, *H*-2b,1a & 1b), 2.63 (ddt, *J* 15.8, 4.6, 1.6, 1H, *H*-2b), 2.60 – 2.45 (m, 2H, *H*-2a), 1.30 (t, *J* 7.1, 3H, C*H*$_3$), 1.25 (t, *J* 7.1, 3H, C*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) 202.7 (*C*-3b), 198.8 (*C*-5b), 190.7 (*C*-5a), 185.1 (*C*-3a), 170.6 (*C*=O), 168.8 (*C*=O), 137.9 (*C* arom.), 137.0 (*C* arom.), 128.5 (*C*H arom.), 128.4 (*C*H arom.), 127.9 (*C*H arom.), 127.8 (*C*H arom.), 127.7 (*C*H arom.), 127.6 (*C*H arom.), 104.0 (*C*-4a), 73.6 (Ph*C*H$_2$), 73.3 (Ph*C*H$_2$), 72.6 (*C*-7b), 71.2 (*C*-7a), 62.1 (-O*C*H$_2$CH$_3$), 61.5 (-O*C*H$_2$CH$_3$), 58.5 (*C*-6b), 56.7 (*C*-4b), 53.3 (*C*-6a), 41.3 (*C*-2b), 36.9 (*C*-1a), 35.1 (*C*-1b), 32.4 (*C*-2a), 14.1 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 305.1386 $[M + H]^+$ 327.1201 $[M + Na]^+$ ($C_{17}H_{21}O_5$ requires 305.1384, $C_{17}H_{20}NaO_5$ requires 327.1203).

156 – (±)-Ethyl 5-((benzyloxy)methyl)-1-chloro-3-oxocyclohex-3-ene-4-carboxylate



155 (0.5 g, 1.64 mmol) was dissolved in dry chloroform (5 mL) and cooled to 0 °C. Phosphorus trichloride (0.45 g, 3.3 mmol, 0.29 mL) was added dropwise and the reaction mixture stirred at 0 °C for 1 h. A further portion of phosphorus trichloride (0.2 mL) was then added dropwise and the solution warmed to room temperature and stirred for 16 h. The solvent was then removed under reduced pressure and the product purified by column chromatography (10% ethyl acetate/petroleum ether) to give **156** (0.33 g, 63%) as a colourless oil found to be a 1:0.26 mixture of keto/enol tautomers. Data given for the major ketone tautomer; **IR** υ_{max}/cm^{-1} 2861, 1736, 1676, 1615; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 5H, C*H* arom.), 6.17 (m, 1H, *H*-2), 4.43 (d, *J* 11.5, 1H, PhC*H*$_2$), 4.38 (d, *J* 11.5, 1H, PhC*H*$_2$), 4.12 (q, *J* 7.1, 2H, -OC*H*$_2$CH$_3$), 3.41 – 3.31 (m, 3H, *H*-4 & *H*-7), 2.83 – 2.67 (m, 3H, *H*-5 & *H*-6), 1.18 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.7 (*C*-3), 169.1 (*C*=O), 157.9 (*C*-1), 137.7 (*C* arom.), 128.5 (*C*H arom.), 127.9 (*C*H arom.), 127.7 (*C*H arom.), 127.1 (*C*H arom.), 73.4 (Ph*C*H$_2$), 70.5 (*C*-7), 61.4 (-O*C*H$_2$CH$_3$), 55.1 (*C*-4), 37.7 (*C*-5), 36.0 (*C*-6), 14.2 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 323.1044 $[M + H]^+$ 345.0863 $[M + Na]^+$ ($C_{17}H_{20}O_4Cl$ requires 323.1045, $C_{17}H_{19}NaO_4Cl$ requires 345.0864).

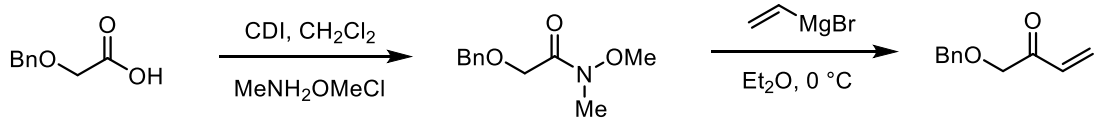
159 and 160 – (±)-Ethyl (1*R*,6*S*)-6-((benzyloxy)methyl)-4-chloro-2-oxo-1-(3-oxobutyl)cyclohex-3-ene-1-carboxylate* and (±)-ethyl (1*S*,5*R*,6*S*,9*S*)-9-((benzyloxy)methyl)-4-chloro-6-hydroxy-6-methyl-2-oxobicyclo[3.3.1]non-3-ene-1-carboxylate*



156 (53 mg, 0.16 mmol) and methyl vinyl ketone (27 µL, 0.33 mmol) were dissolved in methanol and triethylamine (5.0 mg, 7.0 µL, 0.05 mmol) added. The reaction mixture was heated to 60 °C for 5 h then cooled to room temperature and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography (5-20% ethyl acetate/petroleum ether) to give **159** (17.8 mg, 28%) as a colourless oil and **160** (13.1 mg, 21%) as a colourless oil; **159: IR** υ_{max}/cm^{-1} 2922 (w), 1717, 1670, 1621; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H, C*H* arom.), 6.26 (t, *J* 1.5, 1H, *H*-2), 4.47 (s, 2H, PhC*H*$_2$), 4.12 – 3.96 (m, 2H, -OC*H*$_2$CH$_3$), 3.69 (dd, *J* 10.0, 4.0, 1H, *H*-11), 3.53 (dd, *J* 10.0, 7.5, 1H, *H*-11), 2.88 (dd, *J* 8.0, 1.5, 2H, *H*-6), 2.52 – 2.39 (m, 2H, *H*-5 & *H*-7), 2.35 (ddd, *J* 12.0, 10.0, 5.0, 2H, *H*-8), 2.09 (s, 3H, *H*-10), 2.06 (m, 1H, *H*-7), 1.15 (t, *J* 7.0, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.4 (*C*-9), 193.1 (*C*-3), 169.7 (*C*=O), 157.9 (*C*-1), 137.7 (*C* arom.), 128.5 (*C*H arom.),

127.9 (*C*H arom.), 127.8 (*C*H arom.), 127.8 (*C*H arom.), 73.4 (Ph*C*H$_2$), 69.4 (*C*-11), 61.7 (-O*C*H$_2$CH$_3$), 57.2 (*C*-4), 40.2 (*C*-5), 38.4 (*C*-8), 35.9 (*C*-6), 29.9 (*C*-10), 24.8 (*C*-7), 14.0 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 393.1467 [M + H]$^+$ ($C_{21}H_{26}O_5Cl$ requires 393.1463). **160: IR** υ_{max}/cm^{-1} 3498 (br), 2934 (w), 1732, 1674, 1605; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 5H, C*H* arom.), 6.32 (s, 1H, *H*-2), 4.42 (d, *J* 11.9, 1H, PhC*H*$_2$), 4.36 (d, *J* 11.9, 1H, PhC*H*$_2$), 4.05 (q, *J* 7.1, 2H, -OC*H*$_2$CH$_3$), 3.48 (dd, *J* 9.8, 5.9, 1H, *H*-11), 3.42 (dd, *J* 9.8, 8.9, 1H, *H*-11), 3.11 (ddd, *J* 8.9, 5.9, 2.6, 1H, *H*-5), 2.96 (d, *J* 2.6, 1H, *H*-6), 2.32 (td, *J* 13.5, 6.8, 1H, *H*-7), 1.75 (ddd, *J* 13.5, 4.4, 2.7, 1H, *H*-7), 1.58 – 1.46 (m, 2H, *H*-8), 1.34 (s, 3H, *H*-10), 1.12 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.3 (*C*=O), 170.8 (*C*=O), 156.8 (*C*-1), 137.9 (*C* arom.), 130.4 (*C*-2), 128.4 (*C*H arom.), 127.8 (*C*H arom.), 127.7 (*C* arom.), 73.3 (Ph*C*H$_2$), 69.6 (*C*-9), 68.8 (*C*-11), 61.3 (-O*C*H$_2$CH$_3$), 56.1 (*C*-4), 53.6 (*C*-6), 42.6 (*C*-5), 31.3 (*C*-8), 30.2 (*C*-10), 28.9 (*C*-7), 14.0 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 393.1465 [M + H]$^+$ ($C_{21}H_{26}O_5Cl$ requires 393.1463).

161 – 1-(Benzyloxy)but-3-en-2-one

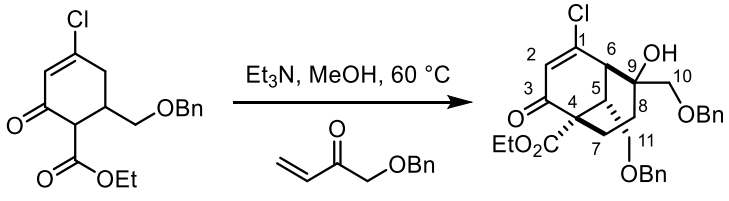


162 **161**

CDI (0.54 g, 3.3 mmol) was added to a solution of 2-(benzyloxy)acetic acid (0.43 mL, 3.00 mmol) in DCM (10 mL) at room temperature. After 1 h, N,O-dimethylhydroxylamine (0.32 g, 0.3 mmol) was added and the reaction stirred for a further 6.5 h. The reaction was quenched with aqueous hydrochloric acid (1.0 M, 10 mL) and stirred for 10 min. The aqueous layer was extracted with DCM (3 × 10 mL) and the combined organic extracts dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (50% ethyl acetate/petroleum ether) to give **162** (0.27 g, 43%) as a colourless oil which was used immediately in the next step. **162** (0.27 g, 1.3 mmol) was dissolved in diethyl ether (6.0 mL) and cooled to 0 °C. Vinyl magnesium bromide (1.0 M in THF, 3.20 mL, 3.20 mmol) was added dropwise and the reaction mixture stirred at 0 °C for 30 min before warming to room temperature. After a further 1.5 h, the solution was cooled to 0 °C and acetone (0.65 mL) added, followed by hydrochloric acid (3.0 M, 2 mL) and then the aqueous phase extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography to give the product **161** (85 mg, 37%) as a colourless oil; **IR** υ_{max}/cm^{-1} 2923 (w), 2861 (w), 1736, 1677,1615 (w); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29

– 7.42 (m, 5H, C*H* arom.), 6.58 (dd, *J* 17.6, 10.7, 1H, *H*-2), 6.37 (dd, *J* 17.6, 1.3, 1H, *H*-1), 5.85 (dd, *J* 10.7, 1.3, 1H, *H*-1), 4.65 (s, 2H, *H*-4), 4.30 (s, 2H, PhCH_2); **HRMS** (ESI+) 199.0729 $[M+Na]^+$ 215.0475 $[M+K]^+$ ($C_{11}H_{12}O_2Na$ requires 199.0735, $C_{11}H_{12}O_2K$ requires 215.0474). Data in accordance with literature.[212]

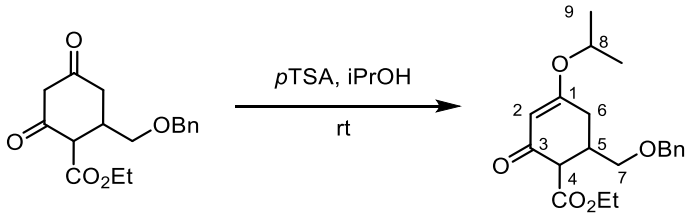
163 – (±)-Ethyl (1S,5R,6R,9S)-6,9-bis((benzyloxy)methyl)-4-chloro-6-hydroxy-2-oxobicyclo[3.3.1]-non-3-ene-1-carboxylate*



156 **161** **163**

156 (0.10 g, 0.31 mmol) and **161** (60 mg, 0.34 mmol) were dissolved in methanol (2 mL) and triethylamine (13 µL, 0.09 mmol) added before heating to 60 °C. After 7 h, the solvent was removed under reduced pressure and the product purified by column chromatography (10% ethyl acetate/petroleum ether) to give **163** (52.2 mg, 34%) as a colourless oil; **IR** υ_{max}/cm^{-1} 3493 (br, w), 1936, 1865, 1731 (s), 1673 (s), 1604; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.14 (m, 10H, C*H* arom.), 6.31 (s, 1H, O*H*), 4.54 (d, *J* 11.5, 1H, PhCH_2), 4.44 (d, *J* 11.5, 1H, PhCH_2), 4.40 (d, *J* 12.0, 1H, PhCH_2), 4.34 (d, *J* 12.0, 1H, PhCH_2), 4.03 (q, *J* 7.1, 2H, -OCH_2CH$_3$), 3.53 – 3.36 (m, 3H, *H*-10 & *H*-11), 3.31 – 3.21 (m, 2H, *H*-6 & *H*-10), 3.10 (ddd, *J* 9.0, 6.0, 2.5, 1H, *H*-5), 2.36 (ddd, *J* 14.5, 13.5, 5.0, 1H, *H*-7), 1.74 (ddd, *J* 13.5, 5.0, 2.1, 1H, *H*-7), 1.58 (ddd, *J* 14.5, 5.0, 2.1, 1H, *H*-8), 1.35 (td, *J* 14.5, 5.0, 1H, *H*-8), 1.10 (t, *J* 7.1, 3H, -OCH$_2$CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.3 (*C*-3), 170.7 (*C*=O), 156.4 (*C*-1), 138.0 (*C* arom.), 137.5 (*C* arom.), 131.0 (C-2), 128.5 (*C*H arom.), 128.4 (*C*H arom.), 128.0 (*C*H arom.), 128.0 (*C*H arom.), 127.7 (*C*H arom.), 127.7(*C*H arom.), 75.5 (*C*-10), 73.4 (Ph*C*H$_2$), 73.2 (Ph*C*H$_2$), 70.8 (*C*-9), 68.8 (*C*-11), 61.3 (-O*C*H$_2$CH$_3$), 56.6 (*C*-4), 49.3 (*C*-6), 42.4 (*C*-5), 27.9 (*C*-7), 26.7 (*C*-8), 14.0 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 499.1875 $[M + H]^+$ ($C_{28}H_{32}ClO_6$ requires 499.1882).

165 – (±)-Ethyl 5-((benzyloxy)methyl)-1-isopropoxy-3-oxocyclohex-2-ene-4-carboxylate

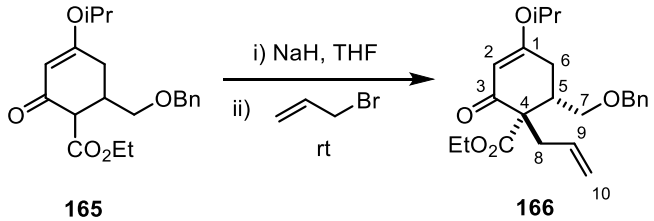


155 **165**

155 (6.79 g, 22.3 mmol) and *p*-toluenesulfonic acid (0.68 g, 3.57 mmol) was dissolved in isopropanol (68 mL) and stirred at room temperature. After 48 h the solvent was removed

under reduced pressure and the resulting oil purified by column chromatography (10-20% ethyl acetate/petroleum ether) to give the product **165** (4.72 g, 61%) as a yellow oil **IR** ν_{max}/cm^{-1} 3675, 2980, 2901, 1736, 1654, 1601; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H, C*H* arom.), 5.37 (s, 1H, *H*-2), 4.54 – 4.38 (m, 3H, PhC*H*$_2$ & *H*-8), 4.20 (q, *J* 7.1, 2H, -OC*H*$_2$CH$_3$), 3.46 – 3.40 (m, 2H, *H*-7), 3.36 (d, *J* 11.2, 1H, *H*-4), 2.78 (m, 1H, *H*-5), 2.50 (d, *J* 7.6, 2H, *H*-6), 1.30 (d, *J* 6.1, 3H, *H*-9), 1.28 (d, *J* 6.1, 3H, *H*-9), 1.26 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.0 (*C*-3), 175.7 (*C*-1), 170.3 (*C*=O), 138.0 (*C* arom.), 128.4 (*C*H arom.), 127.7 (*C*H arom.), 127.6 (*C*H arom.), 101.9 (*C*-2), 73.3 (Ph*C*H$_2$), 71.5 (*C*-8), 71.3 (*C*-7), 61.1 (-O*C*H$_2$CH$_3$), 55.5 (*C*-4), 36.7 (*C*-5), 31.6 (*C*-6), 21.5 (*C*-9), 21.4 (*C*-9), 14.2 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 347.1861 $[M+H]^+$ 369.1681 $[M+Na]^+$ ($C_{20}H_{27}O_5$ requires 347.1853, $C_{20}H_{26}NaO_5$ requires 369.1672).

166 – (±)-Ethyl-(4*S*,5*S*)-5-((benzyloxy)methyl)-4-(prop-2-ene-1-yl)-1-isopropoxy-3-oxocyclohex-2-ene-4-carboxylate

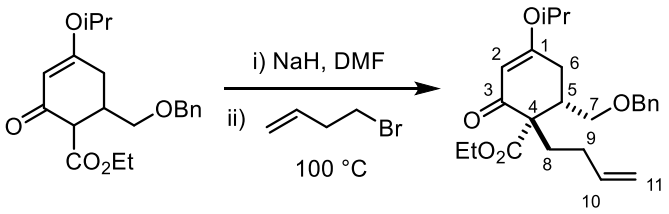


165 **166**

165 (30 mg, 0.087 mmol) was dissolved in anhydrous THF (1.00 mL) and sodium hydride (60% dispersion in mineral oil, 5.2 mg, 0.13 mmol) added in one portion. After 10 min allylbromide (11 µL, 0.13 mmol) was added and the resulting solution stirred at room temperature for a further 24 h before addition of saturated aqueous $NaHCO_3$ (2 mL). The resulting phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to afford the product **166** (24.8 mg, 72%, d.r. > 20:1) as a colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 5H, C*H* arom.), 5.54 (dtd, *J* 17.5, 9.7, 4.9, 1H, *H*-9), 5.43 (d, *J* 1.6, 1H, *H*-2), 5.14 – 4.99 (m, 2H, *H*$_2$-10), 4.45 (s, 2H, PhC*H*$_2$), 4.45 (m, 1H, -C*H*(CH$_3$)$_2$) 4.12 – 3.94 (m, 2H, -OC*H*$_2$CH$_3$), 3.64 (dd, *J* 9.5, 3.3, 1H, H-7), 3.42 (dd, *J* 9.6, 7.4, 1H, H-7), 3.19 (ddt, *J* 14.3, 5.0, 1.7, 1H, H-8), 2.72 (ddd, *J* 18.3, 12.9, 1.5, 1H, H-6), 2.62 – 2.42 (m, 3H, H-5,6,8), 1.30 (d, *J* 6.1, 3H, -CH(C*H*$_3$)$_2$), 1.30 (d, *J* 6.1, 3H, -CH(C*H*$_3$)$_2$), 1.14 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 195.4 (*C*-3), 176.5 (*C*-1), 170.8 (*C*=O), 138.2 (*C* arom.), 133.6 (*C*-9), 128.5 (*C*H arom.), 127.8 (*C*H arom.), 127.7 (*C*H arom.), 119.2 (*C*-10), 102.9 (*C*-2), 73.3 (Ph*C*H$_2$), 71.3 (-*C*H(CH$_3$)$_2$), 69.6 (*C*-7), 61.3 (-O*C*H$_2$CH$_3$), 57.2 (*C*-4), 37.5 (*C*-5), 35.8 (*C*-8), 31.1 (*C*-6), 21.7 (-CH(*C*H$_3$)$_2$), 21.4

(-CH(CH$_3$)$_2$), 14.1 (-OCH$_2$$CH_3$); **HRMS** (ESI$^+$) 387.2167 [M+H]$^+$ 409.1979 [M+Na]$^+$ ($C_{23}H_{31}O_5$ requires 387.2166, $C_{23}H_{30}NaO_5$ requires 409.1985).

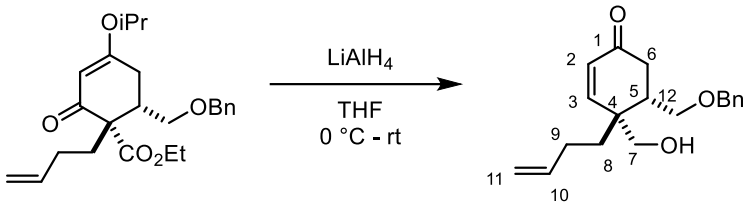
167 – (±)-Ethyl-(4*S*,5*S*)-5-((benzyloxy)methyl)-4-(but-3-en-1-yl)-1-isopropoxy-3-oxocyclohex-2-ene-4-carboxylate



165 **167**

165 (4.32 g, 12.5 mmol) was dissolved in anhydrous DMF (5 mL) and added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.75 g, 18.7 mmol) in DMF (45 mL) at room temperature. After 30 min, 4-bromobut-1-ene (1.9 mL, 18.7 mmol) was added and the solution heated to 100 °C. After 20 h, the reaction was cooled to room temperature and quenched by addition of water (10 mL) and aqueous hydrochloric acid (1.0 M, 10 mL) and the solution extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with water (5 × 20 mL), dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography (20% ethyl acetate/petroleum ether) to give **167** (2.41 g, 48%, d.r. > 20:1) as a colourless oil; **IR** ν_{max}/cm^{-1} 2979, 2925, 1728, 1650, 1604, 1205; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 5H, CH arom.), 5.78 (dddd, J 15.9, 12.9, 6.3, 4.4, 1H, H-10), 5.42 (s, 1H, H-2), 5.00 (m, 1H, H-11), 4.93 (m, 1H, H-11), 4.54 – 4.41 (m, 3H, PhCH_2 & CH(CH$_3$)$_2$), 4.11 – 3.97 (m, 2H, -OCH_2CH$_3$), 3.67 (dd, J 9.5, 3.5, 1H, H-7), 3.47 (dd, J 9.5, 7.9, 1H, H-7), 2.70 – 2.50 (m, 3H, H_2-6 & H-5), 2.43 (m, 1H, H-8), 1.98 (m, 1H, H-9), 1.91 – 1.81 (m, 2H, H-8 & H-9), 1.30 (d, J 6.1, 3H, -CH(CH_3)$_2$), 1.29 (d, J 6.1, 3H, -CH(CH_3)$_2$), 1.14 (t, J 7.1, 3H, -OCH$_2$CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 195.4 (C-3), 175.9 (C-1), 171.0 (C=O), 138.1 (C-10), 138.1 (C arom.), 128.4 (CH arom.), 127.7 (CH arom.), 127.7 (CH arom.), 114.8 (C-11), 103.0 (C-2), 73.3 (PhCH$_2$), 71.2 (-CH(CH$_3$)$_2$), 70.0 (C-7), 61.1 (-OCH$_2$CH$_3$), 57.7 (C-4), 37.6 (C-5), 31.1 (C-6), 30.2 (C-8), 28.4 (C-9), 21.6 (-CH(CH$_3$)$_2$), 21.4 (-CH(CH$_3$)$_2$), 14.0 (-OCH$_2$$CH_3$); **HRMS** (ESI$^+$) 401.2326 [M+H]$^+$ 423.2149 [M+Na]$^+$ ($C_{24}H_{33}O_5$ requires 401.2323, $C_{24}H_{32}NaO_5$ requires 423.2142).

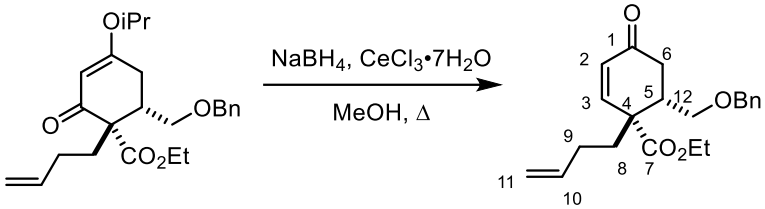
168 – (±)-(4*R*,5*S*)-5-((Benzyloxy)methyl)-4-(but-3-en-1-yl)-4-(hydroxymethyl)cyclohex-2-en-1-one



167 **168**

167 (0.14 g, 0.35 mmol) was dissolved in dry THF (1.0 mL) and cooled to 0 °C. Lithium aluminium hydride (1.0 M in THF, 0.37 mL) was added dropwise and the solution slowly allowed to warm to room temperature. After 6 h, the reaction was cautiously quenched with water (1.0 mL) followed by aqueous hydrochloric acid (1.0 M, 1.0 mL). The aqueous mixture was extracted with diethyl ether (3 × 5 mL) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography (20% ethyl acetate/petroleum ether) to give the **168** (9%, 9.2 mg) as a colourless oil; **IR** ν_{max}/cm^{-1} 3380, 2923, 1640, 1453, 1096, 1068, 1027, 909, 736, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H, C*H* arom.), 6.56 (d, *J* 10.2, 1H, *H*-3), 6.04 (d, *J* 10.2, 1H, *H*-2), 5.80 (ddt, *J* 16.7, 10.2, 6.5, 1H, *H*-10), 5.09 – 4.92 (m, 2H, *H*-11), 4.60 (d, *J* 11.7, 1H, PhCH_2), 4.52 (d, *J* 11.7, 1H, PhCH_2), 3.77 (dd, *J* 10.1, 2.4, 1H, *H*-12), 3.60 (m, 1H, *H*-7), 3.53 – 3.41 (m, 2H, *H*-7 & *H*-12), 2.81 (dd, *J* 17.1, 12.0, 1H, *H*-6), 2.45 – 2.29 (m, 2H, *H*-6 & *H*-5), 2.11 – 1.96 (m, 2H, *H*-9), 1.83 (m, 1H, *H*-8), 1.65 (m, 1H, *H*-8), 1.60 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.4 (*C*-1), 154.9 (*C*-3), 138.0 (*C*-10), 136.7 (*C* arom.), 130.0 (*C*-2), 128.7 (*C* arom.), 128.3 (*C* arom.), 127.9 (*C* arom.), 115.1 (*C*-11), 73.9 (Ph*C*H_2), 69.6 (*C*-12), 64.5 (*C*-7), 44.5 (*C*-4), 39.2 (*C*-5), 38.1 (*C*-6), 33.8 (*C*-8), 28.1 (*C*-9); **HRMS** (ESI^+) 303.1945 $[M+H]^+$ 325.1767 $[M+Na]^+$ ($C_{19}H_{27}O_3$ requires 303.1955, $C_{19}H_{26}NaO_3$ requires 3250.1774).

171 – (±)-Ethyl-(4*R*,5*S*)-5-((benzyloxy)methyl)-4-(but-3-en-1-yl)-1-oxocyclohex-2-ene-4-carboxylate

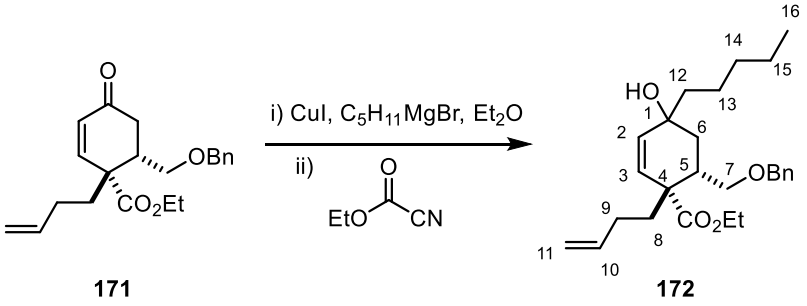


167 **171**

167 (1.39 g, 3.47 mmol) was dissolved in methanol (55 mL) and sodium borohydride (0.39 g, 10.42 mmol) and cerium (III) chloride heptahydrate (1.94 g, 5.21 mmol) added before heating the reaction mixture at reflux. After 16 h, the reaction was quenched with aqueous hydrochloric acid (3.0 M, 20 mL) and then extracted with ethyl acetate (3 × 50 mL). The combined organic

layers were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography (20% diethyl ether/petroleum ether) to give the product **171** (0.43 g, 36%) as a colourless oil; **IR** ν_{max}/cm^{-1} 3684, 3674, 2987, 2971, 2900, 1728, 1682, 1075, 1056; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H, C*H* arom.), 7.06 (dd, *J* 10.4, 1.0, 1H, *H*-3), 6.07 (d, *J* 10.4, 1H, *H*-2), 5.79 (m, 1H, *H*-10), 5.10 – 4.96 (m, 2H, *H*-11), 4.44 (s, 2H, PhCH_2), 4.20 – 4.00 (m, 2H, -OCH_2CH$_3$), 3.50 (m, 1H, *H*-12), 3.40 (dd, *J* 9.6, 7.1, 1H, *H*-12), 2.71 (dd, *J* 5.7, 2.6, 2H, H_2-6), 2.64 (m, 1H, *H*-5), 2.16 – 1.92 (m, 4H, H_2-8 & H_2-9), 1.22 (t, *J* 7.1, 3H, -OCH$_2$CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 197.9 (*C*-1), 172.3 (*C*-7), 150.0 (*C*-3), 137.9 (*C* arom.), 137.3 (*C*-10), 129.3 (*C*-2), 128.4 (*C*H arom.), 127.7 (*C*H arom.), 127.6 (*C*H arom.), 115.5 (*C*-11), 73.3 (Ph*C*H$_2$), 70.1 (*C*-12), 61.3 (-O*C*H$_2$CH$_3$), 49.6 (*C*-4), 41.9 (*C*-5), 37.6 (*C*-8), 37.3 (*C*-6), 28.9 (*C*-9), 14.1 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 343.1896 $[M+H]^+$ 365.1717 $[M+Na]^+$ ($C_{21}H_{27}O_4$ requires 343.1904, $C_{21}H_{26}NaO_4$ requires 365.1723)

172 – (±)-Ethyl (4*R*,5*S*)-5-((benzyloxy)methyl)-4-(but-3-en-1-yl)-1-hydroxy-1-pentylcyclohex-2-ene-4-carboxylate

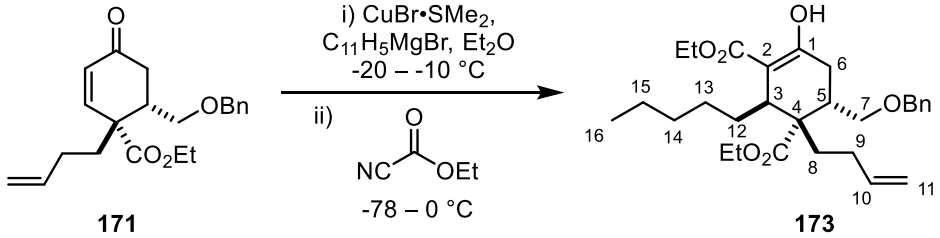


171 **172**

Copper iodide (14.4 mg, 0.15 mmol) was added to a solution of pentylmagnesium bromide (2.0 M in diethyl ether, 0.16 mL, 0.32 mmol) in diethyl ether (1.0 mL) at 0 °C. After 1 h, the solution was warmed to room temperature and a solution of **171** (50 mg, 0.15 mmol) in diethyl ether (1.0 mL) was added dropwise. After 5 h, ethyl cyanoformate (30 μL, 0.32 mmol) was added dropwise and the reaction mixture stirred at room temperature for 17 h. The reaction was then quenched by addition of water (2 mL) and extracted with diethyl ether (2 × 5 mL). The combined organics were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give only the 1,2-addition product **172** (59%, 36 mg) as a colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.86 (d, *J* 10.3, 1H, *H*-3), 5.83 – 5.67 (m, 2H, *H*-2 & *H*-10), 5.04 – 4.92 (m, 2H, *H*-11), 4.45 (s, 2H, PhCH_2), 4.15 – 3.99 (m, 2H, -OCH_2CH$_3$), 3.58 (dd, *J* 9.5, 4.1, 1H, *H*-7), 3.51 (dd, *J* 9.5, 6.8, 1H, *H*-7), 2.20 – 1.97 (m, 3H, *H*-5,6,9), 1.97 – 1.80 (m, 2H, *H*-8 & *H*-9), 1.74 (ddd, *J* 13.0, 11.9, 5.2, 1H, *H*-8), 1.55 – 1.23 (m, 8H, *H*-12,13,14,15), 1.19 (t, *J* 7.1, 3H, -OCH$_2$CH_3), 0.88 (t, *J* 6.9, 3H, *H*-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1 (*C*=O),

138.1 (*C*-10), 137.8 (*C* arom.), 134.2 (*C*-3), 128.9 (*C*-2), 128.4 (*C*H arom.), 127.7 (*C*H arom.), 127.6 (*C*H arom.), 114.8 (*C*-11), 73.3 (Ph*C*H$_2$), 71.4 (*C*-7), 68.9 (*C*-1), 60.7 (-O*C*H$_2$CH$_3$), 48.8 (*C*-4), 41.9 (*C*-12), 39.5 (*C*-5), 38.2 (*C*-8), 35.7 (*C*-6), 32.4 (*C*H$_2$), 28.9 (*C*-9), 23.1 (*C*H$_2$), 22.7 (*C*H$_2$), 14.2 (-OCH$_2$*C*H$_3$), 14.0 (*C*-16); **HRMS** (ESI$^+$) 397.2747 [M+H-H$_2$O]$^+$ 437.2642 [M+Na]$^+$ (C$_{26}$H$_{37}$O$_3$ requires 397.2737, C$_{26}$H$_{38}$NaO$_4$ requires 437.2662).

173 – (±)-Diethyl (3*R*,4*R*,5*S*)-5-((benzyloxy)methyl)-4-(but-3-en-1-yl)-1-hydroxy-3-pentylcyclohex-2-ene-2,4-dicarboxylate

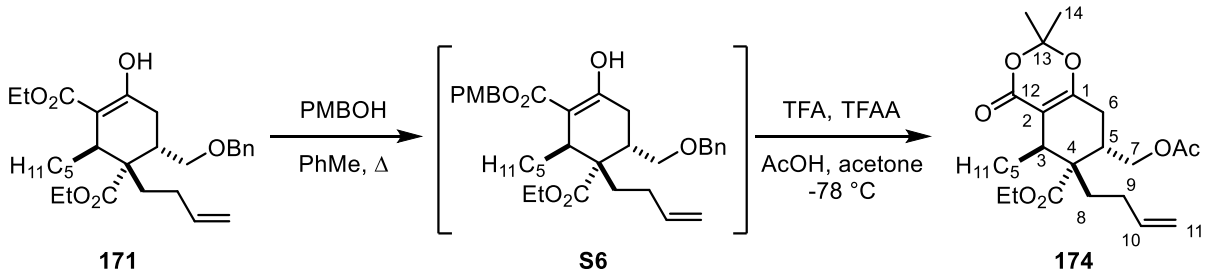


171 **173**

Pentylmagnesium bromide (2.0 M in diethyl ether, 1.16 mL, 2.31 mmol) was added dropwise to a solution of copper bromide dimethylsulfide complex (0.238 g, 1.16 mmol) in diethyl ether (13.5 mL) at -20 °C. The solution was slowly warmed to -10 °C over around 30 min before cooling to -78 °C. **171** (180 mg, 0.53 mmol) in a solution of diethyl ether (3.5 mL) was added dropwise and the solution allowed to warm to -45 °C over 2 h. After this time, the reaction mixture was cooled to -78 °C and ethyl cyanoformate (0.45 mL, 4.86 mmol) was added and stirred for 2 h. The reaction mixture was then warmed to 0 °C, stirred for 30 min and then quenched with aqueous saturated sodium hydrogen carbonate solution (5 mL) and stirred for 1.5 h. The aqueous solution was extracted with diethyl ether (3 × 10 mL) and the combined organics dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography (20% diethyl ether/petroleum ether) to give the product **173** (0.119 g, 46%) as a colourless oil; **IR** ν_{max}/cm^{-1} 2957, 2931, 2870, 1720, 1642, 1264, 1218, 1072; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 12.34 (s, 1H, O*H*), 7.38 – 7.26 (m, 5H, C*H* arom.), 5.77 (ddt, *J* 16.8, 10.2, 6.6, 1H, *H*-10), 5.06 – 4.92 (m, 2H, *H*-11), 4.58 – 4.45 (m, 2H, PhC*H*$_2$), 4.34 – 3.97 (m, 4H, -OC*H*$_2$CH$_3$), 3.95 (m, 1H, *H*-7), 3.76 (dd, *J* 9.0, 8.3, 1H, *H*-7), 3.15 (dd, *J* 10.1, 3.1, 1H, *H*-3), 2.70 (dd, *J* 18.1, 5.8, 1H, *H*-6), 2.40 – 2.21 (m, 2H, *H*-6 & *H*-5), 2.13 – 1.93 (m, 2H, *H*-9), 1.81 (ddd, *J* 14.1, 11.7, 5.0, 1H, *H*-8), 1.62 (m, 1H, *H*-8), 1.47 (m, 1H, *H*-12), 1.32 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$), 1.29 – 1.24 (m, 7H, *H*-12 & *H*$_2$-13,14,15), 1.12 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$), 0.87 (t, *J* 6.9, 3H, *H*-16); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 174.8 (*C*=O), 172.6 (*C*=O), 171.7 (*C*-1), 138.5 (*C* arom.), 138.1 (*C*-10), 128.5 (*C*H arom.), 127.8 (*C*H arom.), 127.7 (*C*H arom.), 114.9 (*C*-11), 103.1 (*C*-1), 73.4 (Ph*C*H$_2$), 72.3 (*C*-7), 60.4 (-O*C*H$_2$CH$_3$), 60.2 (-O*C*H$_2$CH$_3$), 51.6 (*C*-4), 37.6 (*C*-5), 36.6 (*C*-3), 34.2 (*C*-8), 32.8

(*C*-12), 32.7 (*C*-6), 32.6 (*C*-13/14), 28.9 (*C*-9), 27.7 (*C*-13/14), 22.8 (*C*-15), 14.4 (-OCH$_2$*C*H$_3$), 14.2 (-OCH$_2$*C*H$_3$), 14.2 (*C*-16); **HRMS** (ESI$^+$) 487.3063 [M+H]$^+$ 509.2885 [M+Na]$^+$ ($C_{29}H_{43}O_6$ requires 487.3054, $C_{29}H_{42}NaO_6$ requires 509.2874).

174 – (±)-Ethyl (3*R*,4*R*,5*S*)-5-((acetyl)methyl)-4-(but-3-en-1-yl)-13,13-dimethyl-1-oxo-3-pentyltetrahydro-4*H*-benzodioxine-4-carboxylate

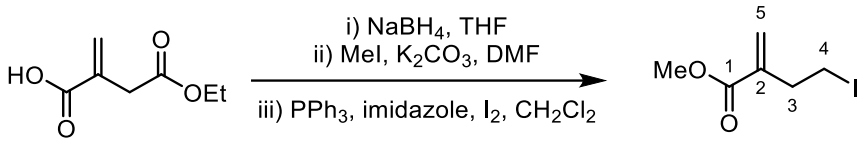


171 **S6** **174**

171 (28 mg, 58 μmol) and *p*-methoxybenzyl alcohol (43 μL, 0.35 mmol) were dissolved in toluene (3 mL) and heated at reflux with Dean-Stark apparatus. After 48 h, the solution was cooled to room temperature and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography (10% ethyl acetate/petroleum ether) to give **S6** (47 mg) which was immediately used in the next step. **S6** (5.0 mg, 86 μmol) was dissolved in dry acetone (0.35 mL) and cooled to 0 °C. TFAA (75 μL, 0.54 mmol) was added dropwise followed by acetic anhydride (58 μL, 0.62 mmol) and TFA (0.35 mL). The solution was slowly allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (2 mL) then solid sodium hydrogen carbonate added until neutralised. The aqueous solution was extracted with ethyl acetate (3 × 5 mL) and the organics dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product **174** (89%, 3.8 mg) as a colourless oil; **IR** ν_{max}/cm^{-1} 3394, 2971, 1703, 1655, 1249, 1038; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* 17.0, 10.1, 6.4, 1H, *H*-10), 5.05 (dq, *J* 17.0, 1.6, 1H, *H*-11), 5.00 (dq, *J* 10.1, 1.6, 1H, *H*-11), 4.66 (dd, *J* 11.0, 4.2, 1H, *H*-7), 4.40 (dd, *J* 11.0, 8.9, 1H, *H*-7), 4.16 (dq, *J* 10.7, 7.1, 1H, -OC*H*$_2$CH$_3$), 4.07 (dq, *J* 10.7, 7.1, 1H, -OC*H*$_2$CH$_3$), 3.34 (dd, *J* 10.7, 3.2, 1H, *H*-3), 2.47 (dd, *J* 18.5, 6.3, 1H, *H*-6), 2.39 (m, 1H, *H*-5), 2.28 (dd, *J* 18.5, 10.4, 1H, *H*-6), 2.14 – 2.06 (m, 2H, *H*-9), 2.09 (s, 3H, -COC*H*$_3$), 1.92 (m, 1H, *H*-8), 1.70 (m, 1H, *H*-8), 1.69 (s, 3H, *H*-14), 1.65 (s, 3H, *H*-14), 1.56 (m, 1H, C*H*$_2$), 1.49 – 1.18 (m, 7H, C*H*$_2$), 1.21 (t, *J* 7.1, 3H, OCH$_2$C*H*$_3$), 0.90 (t, *J* 7.1, 3H, C*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.0 (*C*=O), 170.9 (*C*=O), 163.2 (*C*-1), 161.2 (*C*-12), 137.6 (*C*-10), 115.1 (*C*-11), 107.6 (*C*-2), 105.1 (*C*-13), 65.8 (*C*-7), 60.8 (-O*C*H$_2$CH$_3$), 51.6 (*C*-4), 36.6 (*C*-5), 35.4 (*C*-3), 33.5 (*C*-8), 32.4 (*C*H$_2$), 32.1 (*C*H$_2$), 30.4 (*C*-6), 28.6 (*C*-9), 27.4 (*C*H$_2$), 26.9 (*C*-14), 23.4 (*C*-14), 22.5 (*C*H$_2$), 21.0

(C(O)*C*H$_3$), 14.1 (*C*H$_3$), 14.0 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 451.2699 [M+H]$^+$ 473.2552 [M+Na]$^+$ ($C_{25}H_{39}O_7$ requires 451.2696, $C_{25}H_{38}NaO_7$ requires 473.2515).

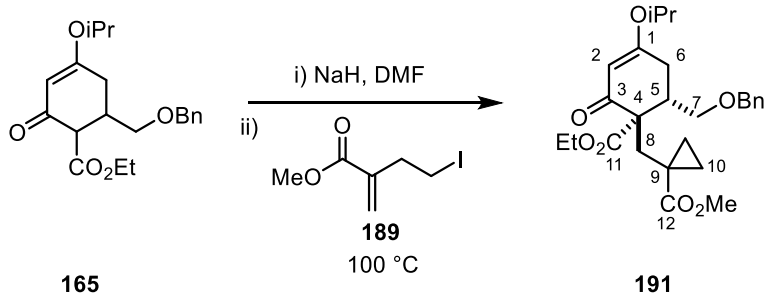
189 – Methyl 4-iodo-2-methylenebutanoate



187 **189**

Monoethyl itaconate (1.00 g, 6.32 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. Sodium borohydride (1.20 g, 31.6 mmol) was added in portions over 10 min and stirred at 0 °C for 30 min. Water (11.7 mL) was added dropwise over 5 min and the solution warmed to 40 °C. After 20 h, the reaction was cooled to room temperature and hydrochloric acid (3.0 M, 10 mL) added. The solution was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting white solid was purified by column chromatography (50:49:1 ethyl acetate/petroleum ether/acetic acid) to give 4-hydroxy-2-methylenebutanoic acid (0.24 g, 33%) which was carried through to the subsequent step. Methyl iodide (0.12 mL, 1.85 mmol) was added to a solution of 4-hydroxy-2-methylenebutanoic acid (215 mg, 1.85 mmol) and potassium carbonate (0.51 g, 3.70 mmol) in DMF (1.9 mL) at room temperature. After stirring for 2 h, the reaction was quenched by addition of water (3 mL), extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent remoed under reduced pressure. The resulting oil was dissolved in anhydrous DCM and triphenyl phosphine (0.73 g, 2.78 mmol), imidazole (63 mg, 0.93 mmol) and iodine (1.41 g, 5.55 mmol) added. After 3 h at room temperature, sodium thiosulfate (5 mL) was added and the solution stirred for ca. 20 min. The solution was washed with further sodium thiosulfate (3 × 10 mL) and the organic layer dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product **189** as a colourless oil (120 mg, 27%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.27 (d, *J* 1.1, 1H, *H*-5), 5.63 (d, *J* 1.1, 1H, *H*-5), 3.73 (s, 3H, C*H*$_3$), 3.28 (t, *J* 7.3, 2H, *H*-4), 2.82 (t, *J* 7.3, 2H, *H*-3). Due to its instability, **189** was carried through to the subsequent step without pursuing full characterisation.

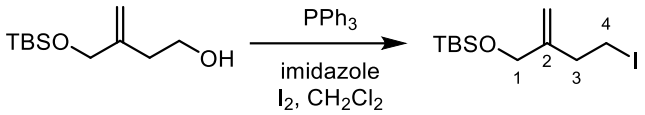
191 – (±)-Ethyl-(4*S*,5*S*)-5-((benzyloxy)methyl)-1-isopropoxy-4-((1-(methoxycarbonyl)cyclopropyl)-methyl)-3-oxocyclohex-2-ene-4-carboxylate



165 **191**

165 (120 mg, 0.35 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 14 mg, 0.35 mmol) in DMF (2 mL) and allowed to stir at room temperature for 30 min. A solution of **189** (100 mg, 0.42 mmol) in DMF (0.5 mL) was added and the solution heated to 100 °C for 17 h before cooling to room temperature. The reaction was quenched by addition of water (2 mL) followed by aqueous hydrochloric acid (3.0 M, 2 mL). The solution was extracted with diethyl ether (3 × 5 mL) and the combined organic extracts dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography (10% ethyl acetate/petroleum ether) to give cyclopropane **191** (69.5 mg, 44%) as the major product; **IR** ν_{max}/cm^{-1} 3660, 2980 1722, 1646, 1605, 1205, 748; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H, C*H* arom.), 5.44 (s, 1H, *H*-2), 4.53 – 4.40 (m, 3H, -OC*H*$(CH_3)_2$ & -OC*H*$_2$Ph), 4.08 – 3.91 (m, 2H, -OC*H*$_2CH_3$), 3.80 (dd, *J* 9.0, 2.8, 1H, *H*-7), 3.57 (s, 3H, -OC*H*$_3$), 3.39 (dd, *J* 9.0, 7.4, 1H, *H*-7), 3.10 (d, *J* 15.5, 1H, *H*-8), 2.72 (m, 1H, *H*-6), 2.62 – 2.47 (m, 2H, *H*-5,6), 2.38 (d, *J* 15.5, 1H, *H*-8), 1.31 (*app.* t, *J* 6.3, 6H, -OCH(C*H*$_3)_2$), 1.26 (m, 1H, *H*-10), 1.10 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$), 1.06 (dd, *J* 7.5, 2.3, 1H, *H*-10), 0.89 – 0.79 (m, 2H, *H*-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.9 (*C*-3), 176.1 (*C*-1), 175.7 (*C*-12), 170.8 (*C*-11), 138.3 (*C* arom.), 128.4 (*C*H arom.), 127.7 (*C*H arom.), 127.7 (*C*H arom.), 103.0 (*C*-2), 73.4 (O*C*H$_2$Ph), 71.2 (-O*C*H$(CH_3)_2$), 70.6 (*C*-7), 61.3 (-O*C*H$_2CH_3$), 57.7 (*C*-4), 52.0 (O*C*H$_3$), 38.0 (*C*-5), 34.2 (*C*-8), 31.1 (*C*-6), 21.6 (-OCH(*C*H$_3)_2$), 21.4 (-OCH(*C*H$_3)_2$), 20.8 (*C*-9), 20.1 (*C*-10), 14.0 (-OCH$_2$*C*H$_3$), 13.1 (*C*-10); **HRMS** (ESI$^+$) 459.2364 $[M+H]^+$ 481.2201 $[M+Na]^+$ ($C_{26}H_{35}O_7$ requires 459.2377 $C_{26}H_{34}NaO_7$ requires 481.2197).

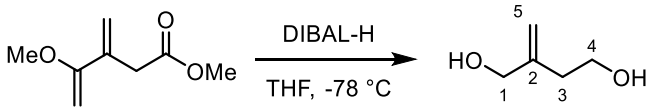
193 – *tert*-Butyl(4-iodo-2-methylenebutoxy)dimethylsilane



196 **193**

196 (1.99 g, 9.2 mmol) was dissolved in anhydrous THF (80 mL) and cooled to 0 °C. Imidazole (1.57 g, 23.0 mmol) and triphenyl phosphine (2.89 g, 11.0 mmol) were added followed by addition of iodine (3.03 g, 12.0 mmol) in portions. The resulting brown solution was warmed to room temperature and stirred for 1 h. The mixture was diluted with hexane (80 mL), filtered through celite and the filtrate concentrated under reduced pressure to give an orange oil which was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product **193** (2.5 g, 83%) as a colourless oil; **IR** ν_{max}/cm^{-1} 3674, 2955, 2958, 2900, 2856, 1080, 836; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.15 (dq, *J* 1.6, 0.8, 1H), 4.95 – 4.91 (m, 1H), 4.12 (d, *J* 1.5, 2H), 3.29 (t, *J* 7.6, 2H), 2.65 (ddd, *J* 8.4, 7.4, 1.1, 2H), 0.94 (s, 9H), 0.10 (s, 6H); Data in accordance with literature.[192]

195 – 2-Methylenebutane-1,4-diol



194 **195**

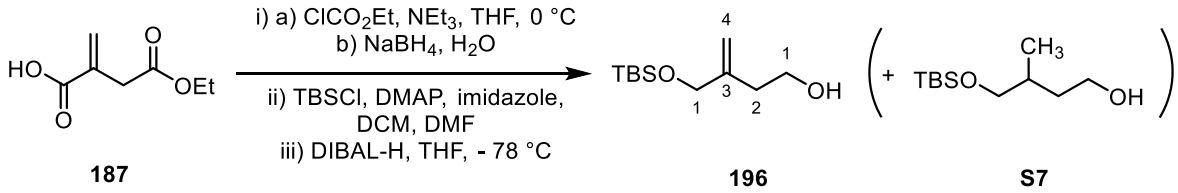
Dimethyl itaconate **194** (1.79 g, 11.3 mmol) was dissolved in THF (75 mL) and cooled to -78 °C. Diisobutylaluminium hydride (1.0 M in hexanes, 50 mL) was added dropwise over 1 h and then the reaction stirred at -78 °C for 1 h before warming to room temperature. After 16 h, the reaction was cooled to 0 °C and quenched with water (20 mL) then a saturated aqueous solution of Rochelle salt (100 mL) and stirred for 1 h. The organics were extracted with ethyl acetate (3 × 100 mL), dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (75% ethyl acetate/petroleum ether) to give the product **195** (0.86 g, 74%) as a colourless oil; **IR** ν_{max}/cm^{-1} 3306 (br), 2888, 1652 (w), 1436, 1017; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.10 (s, 1H, *H*-5), 4.96 (s, 1H, *H*-5), 4.08 (s, 2H, *H*-1), 3.74 (t, *J* 6.0, 2H, *H*-4), 3.05 (s, 2H, -O*H*), 2.36 (t, *J* 6.0, 2H, *H*-3); Data in accordance with literature.[213]

196 – 3-(((*tert*-Butyldimethylsilyl)oxy)methyl)but-3-en-1-ol

195 **196**

tert-Butyldimethylsilylchloride (0.59 g, 3.93 mmol) was added to a solution of imidazole (0.28 g, 4.10 mmol), dimethylaminopyridine (22 mg, 0.18 mmol) and 2-methylenebutane-1,4-diol (0.36 g, 3.57 mmol) in DCM (15 mL) and DMF (15 mL) at -78 °C. After 1 h, the reaction was warmed to room temperature and stirred for a further 45 min. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (20 mL), extracted with DCM (3 × 20 mL) and the combined aqueous layers washed with water (3 × 20 mL). The organics were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product **196** (0.23 g, 30%) as a colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.12 (*app.* q, *J* 1.5, 1H, *H*-4), 4.94 (m, 1H, *H*-4), 4.10 (t, *J* 1.1, 2H, *H*-5), 3.72 (*app.* q, *J* 6.0, 2H, *H*-1), 2.34 (td, *J* 6.0, 1.5, 2H, *H*-2), 0.91 (s, 9H, -OSi(CH_3)$_2$C(CH_3)$_3$), 0.09 (s, 6H, -OSi(CH_3)$_2$C(CH_3)$_3$); **MS** (ESI^+) 217.2 $[M+H]^+$ 239.1 $[M+Na]^+$ ($C_{11}H_{25}O_2Si$ requires 217.2, $C_{11}H_{24}NaO_2Si$ requires 239.1). Data in accordance with literature.[192]

196 – 3-(((*tert*-Butyldimethylsilyl)oxy)methyl)but-3-en-1-ol



187 **196** **S7**

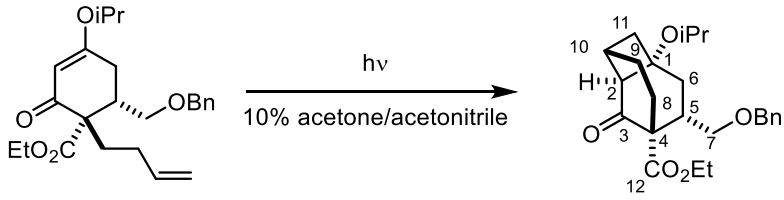
A solution of ethyl chloroformate (1.5 mL, 15.8 mmol) in THF (5 mL) was added to a solution of monoethyl itaconate (2.5 g, 15.8 mmol) and triethylamine (2.2 mL) in THF (15 mL) at 0 °C. After 1 h, the resulting suspension was filtered and added dropwise to a solution of sodium borohydride (1.08 g, 28.5 mmol) in water (7.5 mL) over 30 min. After a further 2 h the reaction was quenched by addition of hydrochloric acid (3.0 M, 15 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (40% diethyl ether/petroleum ether) to give a colourless oil (0.84 g) found to be an inseparable mixture of the ethyl 3-(hydroxymethyl)but-3-enoate (63%) and the saturated alcohol (37%). The mixture was carried through subsequent steps without further purification.

Ethyl 3-(hydroxymethyl)but-3-enoate (1.44 g, 10.0 mmol) was dissolved in anhydrous DMF (50 mL) and imidazole (1.64 g, 24.0 mmol) and *tert*-butyldimethylsilyl chloride (1.81 g, 12.0 mmol) added at room temperature. The resulting solution was stirred for 16 h before partitioning between diethyl ether and water. The organic layer was washed with water (5 × 50 mL), dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure

to give ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)but-3-enoate (2.53 g, 98%, 1:0.6 unsaturated:saturated)

Ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)but-3-enoate (2.85 g) was dissolved in anhydrous DCM (100 mL) and cooled to -15 °C. A solution of diisobutylaluminium hydride (1.0 M in hexanes, 23.2 mL) was added dropwise over 30 min and the resulting solution stirred for a further 1 h. Water (0.9 mL) was added, followed by aqueous sodium hydroxide solution (2.0 M, 1.5 mL) and then water (2 mL). The solution was warmed to room temperature and stirred for 15 min. Magnesium sulfate was added and the suspension stirred for a further 15 min before the suspension was filtered and the solvent removed under reduced pressure to give a 1:0.6 mixture of **196** and **S7** (1.99 g, 83%) as a colourless oil; **IR** ν_{max}/cm^{-1} 3523, 2954, 2929, 2886, 2857, 1253, 1095, 833, 734 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.10 (q, *J* 1.6, 1H), 4.92 (dt, *J* 1.9, 0.9, 1H), 4.08 (t, *J* 1.0, 2H), 3.70 (t, *J* 6.1, 2H), 2.32 (td, *J* 6.1, 1.2, 2H), 0.90 (s, 9H), 0.07 (s, 6H). Data in accordance with literature.[192]

200 – (±)-Ethyl (1*R*,2*S*,4*S*,5*S*,10*S*)-5-((benzyloxy)methyl)-1-isopropoxy-3-oxotricyclo[4.2.2.0^{1,2}]-decane-4-carboxylate

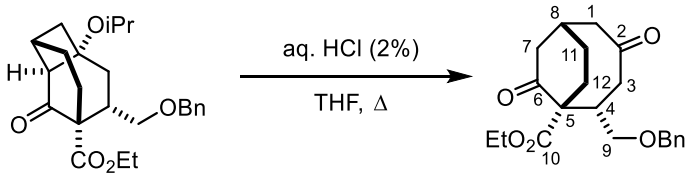


167 **200**

167 (1.0 g, 2.50 mmol) was dissolved in 10% acetone in acetonitrile (150 mL) and irradiated using a 125 W Hg medium pressure UV lamp. After 7.5 h, irradiation was stopped and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography to the product **200** (1.0 g, quant.) as colourless crystals (recrystallised from methanol); **IR** ν_{max}/cm^{-1} 2974, 1734, 1702, 1605, 1109, 731; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H, C*H* arom.), 4.48 (d, *J* 11.9, 1H, PhC*H*$_2$), 4.41 (d, *J* 11.9, 1H, PhC*H*$_2$), 4.21 – 4.05 (m, 2H, -OC*H*$_2$CH$_3$), 3.73 (t, *J* 8.5, 1H, H-7), 3.68 (h, *J* 6.1, 1H, -C*H*(CH$_3$)$_2$), 3.56 (dd, *J* 8.5, 6.9, 1H, *H*-7), 3.06 (d, *J* 10.6, 1H, *H*-2), 3.02 – 2.86 (m, 2H, *H*-5,10), 2.71 (dd, *J* 12.0, 1.1, 1H, *H*-11), 2.51 (ddd, *J* 14.5, 8.5, 2.7, 1H, *H*-8), 2.26 (ddd, *J* 14.5, 10.3, 8.7, 1H, *H*-8), 2.09 – 1.97 (m, 2H, *H*-9,11), 1.84 (dd, *J* 13.1, 3.6, 1H, *H*-6), 1.75 (m, 1H, *H*-9), 1.66 (m, 1H, *H*-6), 1.21 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$), 1.11 (*app.* t, *J* 6.3, 6H, CH(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.6 (*C*-3), 171.0 (*C*-12), 138.1 (*C* arom.), 128.4 (*C*H arom.), 127.6 (*C*H arom.), 127.4 (*C*H arom.), 78.7 (*C*-1), 73.1 (Ph*C*H$_2$), 72.5 (*C*-7), 65.7 (-*C*H(CH$_3$)$_2$), 60.7 (-O*C*H$_2$CH$_3$), 59.5 (*C*-4),

52.7 (*C*-2), 41.5 (*C*-11), 38.5 (*C*-5), 37.4 (*C*-8), 35.9 (*C*-6), 27.3 (*C*-10), 24.6 (-CH(*C*H$_3$)$_2$), 23.7 (*C*-9), 14.1 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 423.2152 [M+Na]$^+$ ($C_{24}H_{32}NaO_5$ requires 423.2142).

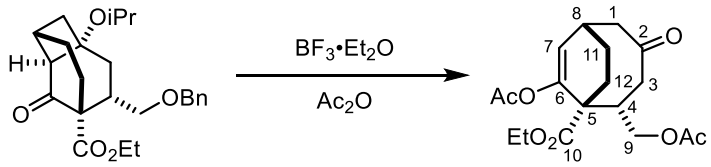
201 – (±)-Ethyl (4*S*,5*S*,8*S*)-4-((benzyloxy)methyl)-2,6-dioxobicyclo[4.2.2]decane-5-carboxylate



200 **201**

200 (54.5 mg, 0.14 mmol) was dissolved in THF (2 mL) and 2% aqueous hydrochloric acid (0.5 mL) and heated to 80 °C. After 90 min, the reaction was diluted with water (2 mL) and extracted with DCM (3 × 3 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give the pure product **201** (47 mg, 96%) as a colourless solid; **m.p.** (ethanol) 116-117 °C; **IR** ν_{max}/cm^{-1} 2931, 1733, 1711, 1240, 1209; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H, C*H* arom.), 4.52 (s, 2H, PhC*H*$_2$), 4.16 – 4.06 (m, 2H, -OC*H*$_2$CH$_3$), 3.71 (dd, *J* 9.8, 3.0, 1H, *H*-9), 3.34 (t, *J* 9.8, 1H, *H*-9), 2.97 (dd, *J* 11.6, 5.2, 1H, *H*-3), 2.77 (m, 1H, *H*-4), 2.73 – 2.66 (m, 3H, *H*-3,7,8), 2.59 (ddd, *J* 14.1, 4.1, 1.9, 1H, *H*-1), 2.53 – 2.42 (m, 2H, H-1,7), 2.41 – 2.30 (m, 2H, *H*-11,12), 2.21 – 2.12 (m, 2H, *H*-11,12), 1.18 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.7 (*C*-2), 207.5 (*C*-6), 172.4 (*C*-10), 138.7 (*C* arom.), 128.2 (*C*H arom.), 127.7 (*C*H arom.), 127.4 (*C*H arom.), 73.0 (Ph*C*H$_2$), 69.4 (*C*-9), 61.5 (-O*C*H$_2$CH$_3$), 59.3 (*C*-5), 52.9 (*C*-1), 44.5 (*C*-7), 44.1 (*C*-4), 40.1 (*C*-3), 30.7 (*C*-11), 28.2 (*C*-8), 24.8 (*C*-12), 13.9 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 381.1677 [M+Na]$^+$ ($C_{21}H_{26}NaO_5$ requires 381.1672).

202 – (±)-Ethyl (4*S*,5*S*,8*S*)-6-acetoxy-4-(acetoxymethyl)-2-oxobicyclo[4.2.2]dec-7-ene-5-carboxylate

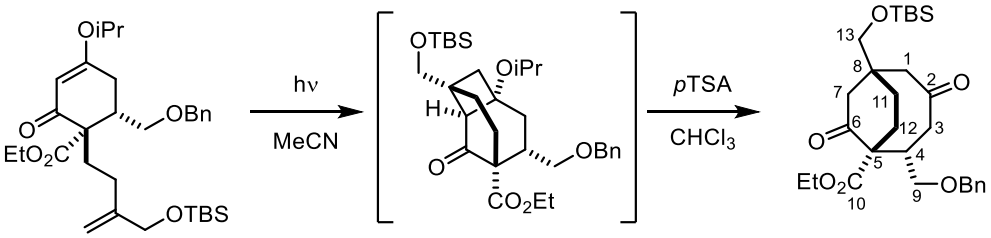


200 **202**

200 (243 mg, 0.61 mmol) was dissolved in acetic anhydride (1.5 mL) and borontrifluoride diethyletherate (78 µL, 0.61 mmol) added dropwise. After 10 min, the reaction was quenched with water (2.0 mL) and extracted with DCM (3 × 5 mL). The organic layers were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was dissolved by column chromatography (35% ethyl acetate/petroleum ether) to give the diacetate **202** (85 mg, 40%) as a colourless oil; **IR** ν_{max}/cm^{-1} 2978, 2937, 1769, 1731, 1696, 1227, 1206; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.11 (d, *J* 7.9, 1H, *H*-7), 4.24 (dd, *J* 11.0, 3.2, 1H, *H*-9), 4.19 – 4.04

(m, 2H, -OC*H*$_2$CH$_3$), 3.82 (dd, *J* 11.0, 9.3, 1H, *H*-9), 2.85 (m, 1H, *H*-8), 2.72 – 2.47 (m, 5H, H-1,3,4), 2.14 (m, 1H, *H*-12), 2.07 (s, 3H, -C*H*$_3$), 2.01 (s, 3H, -C*H*$_3$), 1.97 – 1.70 (m, 3H, *H*-11,12), 1.20 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 212.8 (*C*-2), 172.4 (*C*-10), 170.8 (*C*=O), 167.9 (*C*=O), 144.1 (*C*-6), 122.1 (*C*-7), 65.5 (*C*-9), 61.3 (-O*C*H$_2$CH$_3$), 52.4 (*C*-3), 49.9 (*C*-5), 44.8 (*C*-4), 42.2 (*C*-1), 33.9 (*C*-12), 30.7 (*C*-8), 25.7 (*C*-11), 21.5 (*C*H$_3$), 21.0 (*C*H$_3$), 14.1 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 375.1418 [M+Na]$^+$ (C$_{18}$H$_{24}$NaO$_7$ requires 375.1414).

204 – (±)-Ethyl (4SR,5SR,8RS)-4-((benzyloxy)methyl)-8-(((tert-butyldimethylsilyl)oxy)methyl)-2,6-dioxobicyclo[4.2.2]decane-5-carboxylate

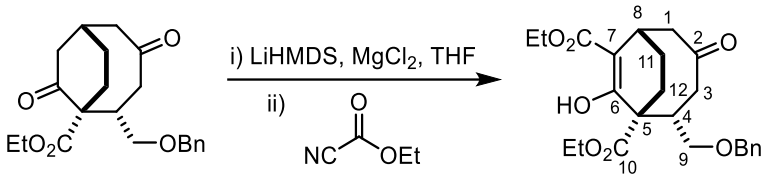


221 **229** **204**

221 (1.0 g, 0.77 mmol) was dissolved in acetonitrile (150 mL) and irradiated with UV light. After 3 h the solvent was removed under reduced pressure to give **229** (1.0 g, quant.). 229 was found to be unstable to column chromatography so was subjected to ring opening immediately.

229 (0.70 g, 1.28 mmol) was dissolved in chloroform (10.0 mL) and *p*TSA (0.24 g, 1.28 mmol) added. The reaction mixture was stirred at room temperature for 20 minutes before adding water (5 mL). The organics were extracted with dichloromethane (3 × 10 mL) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give **204** (0.45 g, 68%) as a colourless oil; **IR** ν_{max}/cm^{-1} 3674, 2987, 2955, 2928, 2900, 2857, 1737, 1714, 1075; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.40 – 7.26 (m, 5H, C*H* arom.), 4.56 (s, 2H, -OC*H*$_2$Ph), 4.20 – 4.07 (m, 2H, -OC*H*$_2$CH$_3$), 3.74 (dd, *J* 9.8, 2.9, 1H, *H*-9), 3.41 (t, *J* 9.8, 1H, *H*-9), 3.30 (d, *J* 9.4, 1H, *H*-13), 3.27 (d, *J* 9.4, 1H, *H*-13) 3.03 (dd, *J* 11.7, 5.5, 1H, *H*-3), 2.79 (dtd, *J* 9.8, 5.5, 2.9, 1H, *H*-4), 2.73 (dd, *J* 11.7, 5.5, 1H, *H*-3), 2.60 (dd, *J* 16.8, 2.0, 1H, *H*-7), 2.46 – 2.26 (m, 4H, *H*-1,7,12), 2.24 – 2.04 (m, 3H, *H*-11,12), 1.21 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$), 0.92 (s, 9H, -OSiC(C*H*$_3$)$_3$(CH$_3$)$_2$), 0.07 (s, 6H, -OSiC(CH$_3$)$_3$(C*H*$_3$)$_2$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ 210.0 (*C*-2), 207.9 (*C*-6), 172.4 (*C*-10), 138.7 (*C* arom.), 128.3 (*C*H arom.), 127.7 (*C*H arom.), 127.4 (*C*H arom.), 73.0 (-O*C*H$_2$Ph), 72.6 (*C*-13), 69.4 (*C*-9), 61.5 (-O*C*H$_2$CH$_3$), 58.9 (*C*-5), 55.6 (*C*-1), 46.9 (*C*-7), 43.8 (*C*-4), 39.9 (*C*-3), 38.5 (*C*-8), 31.2 (*C*-12), 27.5 (*C*-11), 25.8 (-OSiC(*C*H$_3$)$_3$(CH$_3$)$_2$), 18.3 (-OSi*C*(CH$_3$)$_3$(CH$_3$)$_2$), 13.9 (-OCH$_2$*C*H$_3$), -5.5 (-OSiC(CH$_3$)$_3$(*C*H$_3$)$_2$); **HRMS** (ESI$^+$) 525.2640 [M+Na]$^+$ (C$_{28}$H$_{43}$NaO$_6$Si requires 525.2643).

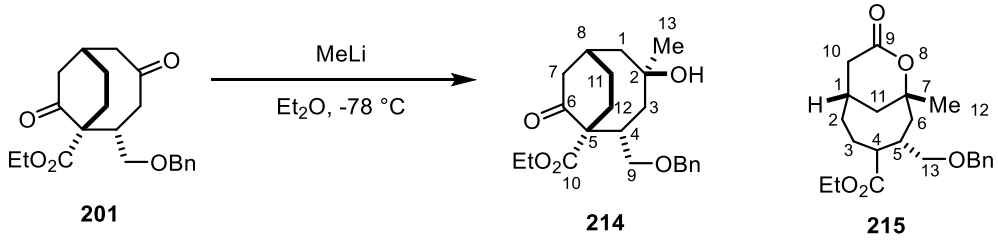
209 – (±)-Diethyl-(4*S*,5*S*,8*S*)4-((benzyloxy)methyl)-6-hydroxy-2-oxobicyclo[4.2.2]dec-7-ene-5,7-dicarboxylate



201 **209**

201 (100 mg, 0.30 mmol) was dissolved in anhydrous THF (1 mL) and cooled to -78 °C. Lithium hexamethyldisilazane (0.30 mL, 1.0 M in THF, 0.30 mmol) was added dropwise and the solution stirred for 15 min at -78 °C. Magnesium chloride (30 mg, 0.32 mmol) was added and the solution stirred for a further 40 min. Ethyl cyanoformate (34 µL, 0.36 mmol) was added and the solution warmed to room temperature. After 18 h, the reaction was quenched with water (2 mL) followed by aqueous hydrochloric acid (2 mL, 3.0 M) and the solution extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography to give **209** (7.9 mg, 6%) as a colourless oil; **IR** ν_{max}/cm^{-1} 3675, 2977, 2928, 2900, 1734, 1696, 1647, 1229; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.51 (s, 1H, O*H*), 7.39 – 7.27 (m, 5H, C*H* arom.), 4.55 (d, *J* 11.9, 1H, -OC*H*$_2$Ph), 4.46 (d, *J* 11.9, 1H, -OC*H*$_2$Ph), 4.29 (m, 2H, -OC*H*$_2$CH$_3$), 4.18 (m, 2H, -OC*H*$_2$CH$_3$), 3.91 (dd, *J* 9.7, 2.8, 1H, *H*-9), 3.27 (t, *J* 9.7, 1H, *H*-9), 3.25 (m, 1H, *H*-8), 2.93 (ddd, *J* 11.5, 4.8, 1.0, 1H, *H*-3), 2.73 (m, 1H, *H*-4), 2.67 (dd, *J* 13.6, 4.2, 1H, *H*-1), 2.57 (dd, *J* 13.6, 4.2, 1H, *H*-1), 2.38 (dd, *J* 11.5, 10.6, 1H, *H*-3), 2.12 (m, 1H, *H*-12), 1.95 – 1.78 (m, 3H, *H*-11,12), 1.34 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$), 1.23 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 213.8 (*C*-2), 172.1 (*C*=O), 171.1 (*C*=O), 169.4 (*C*-6), 138.6 (*C* arom.), 128.3 (*C*H arom.), 127.5 (*C*H arom.), 127.4 (*C*H arom.), 103.9 (*C*-7), 72.7 (-O*C*H$_2$Ph), 71.7 (*C*-9), 61.2 (-O*C*H$_2$CH$_3$), 61.1 (-O*C*H$_2$CH$_3$), 52.1 (*C*-1), 51.7 (*C*-5), 45.6 (*C*-4), 42.9 (*C*-3), 33.6 (*C*-12), 29.3 (*C*-8), 26.6 (*C*-11), 14.3 (-OCH$_2$*C*H$_3$), 14.0 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 453.1889 $[M+Na]^+$ ($C_{24}H_{30}NaO_7$ requires 453.1884).

214 and 215 – (±)-Ethyl (4*S*,5*S*,8*S*)-4-((benzyloxy)methyl)-2-hydroxy-2-methyl-6-oxobicyclo[4.2.2]-decane5-carboxylate and (±)-ethyl (1*S*,7*S*)-5-((benzyloxy)methyl)-7-methyl-9-oxo-8-oxabicyclo-[5.3.1]undecane-4-carboxylate

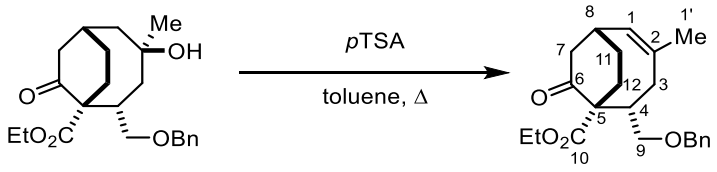


201 **214** **215**

Methyllithium (87 µL, 1.6 M in diethyl ether, 0.14 mmol) was added dropwise to **201** (50 mg, 0.14 mmol) in THF (0.5 mL) and diethyl ether (1.0 mL) at -78 °C and then the solution allowed to slowly warm to room temperature. After 17 h, the reaction was quenched with saturated ammnoium chloride solution (3 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (50% ethyl acetate/petroleum ether) to give **214** (32 mg, 61%) and **215** (16 mg, 31%) both as colourless oils; **214: IR** ν_{max}/cm^{-1} 3675 (br), 2988, 2901, 1726 (w), 1066, 1056; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 5H, C*H* arom.), 4.52 – 4.44 (m, 2H, -OC*H*$_2$Ph), 4.18 – 4.03 (m, 2H, -OC*H*$_2$CH$_3$), 3.73 (dd, *J* 9.5, 2.8, 1H, *H*-9), 3.15 (t, *J* 9.5, 1H, *H*-9), 2.82 (ddd, *J* 15.3, 9.4, 8.2, 1H, *H*-11), 2.64 (m, 1H, *H*-4), 2.57 – 2.44 (m, 2H, *H*-7,8), 2.36 – 2.28 (m, 2H, *H*-3,7), 2.19 – 2.06 (m, 2H, *H*-11,12), 1.96 (dd, *J* 15.4, 6.0, 1H, *H*-1), 1.84 (m, 1H, *H*-12), 1.62 (dd, *J* 15.4, 2.6, 1H, *H*-1), 1.45 (dd, *J* 15.7, 11.0, 1H, *H*-3), 1.26 (s, 3H, *H*-13), 1.20 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.3 (*C*-6), 173.1 (*C*-10), 138.6 (*C* arom.), 128.3 (*C*H arom.), 127.7 (*C*H arom.), 127.5 (*C*H arom.), 72.9 (-O*C*H$_2$Ph), 72.8 (*C*-9), 71.4 (*C*-2), 60.9 (-O*C*H$_2$CH$_3$), 58.9 (*C*-5), 48.0 (*C*-1), 46.6 (*C*-7), 43.6 (*C*-4), 40.4 (*C*-3), 37.0 (*C*-1'), 31.8 (*C*-11), 30.1 (*C*-8), 23.2 (*C*-12), 13.9 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 397.2001 $[M+Na]^+$ ($C_{22}H_{30}NaO_5$ requires 397.1985). **215: IR** ν_{max}/cm^{-1} 3675 (br), 2972, 2901, 1728, 1394, 1251, 1057, 1066; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 5H, C*H* arom.), 4.46 (d, *J* 12.0, 1H, PhC*H*$_2$), 4.42 (d, *J* 12.0, 1H, PhC*H*$_2$), 4.07 (q, *J* 7.0, 2H, -OC*H*$_2$CH$_3$), 4.06 (q, *J* 7.0, 2H, -OC*H*$_2$CH$_3$), 3.30 – 3.18 (m, 2H, *H*-13), 2.65 (dd, *J* 18.1, 7.6, 1H, *H*-10), 2.42 – 2.27 (m, 2H, *H*-10 & *H*-4), 2.27 – 2.19 (m, 2H, H-1 & *H*-11), 2.07 – 1.88 (m, 4H, *H*-2,3,5,6), 1.84 (m, 1H, *H*-6), 1.76 – 1.62 (m, 2H, *H*-3 & *H*-11), 1.55 (m, 1H, *H*-2), 1.40 (s, 3H, *H*-12), 1.21 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.8 (*C*=O), 171.1 (*C*-9), 138.1 (*C* arom.), 128.3 (*C*H arom.), 127.6 (*C*H arom.), 127.5 (*C*H arom.), 84.0 (*C*-7), 74.5 (*C*-13), 73.2 (Ph*C*H$_2$), 60.5 (-O*C*H$_2$CH$_3$), 49.1 (*C*-4),

42.1 (*C*-6), 37.1 (*C*-5), 35.5 (*C*-10), 32.1 (*C*-11), 30.1 (*C*-2), 30.0 (*C*-12), 28.5 (*C*-1), 27.8 (*C*-3), 14.2 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 397.1982 [M+Na]$^+$ ($C_{22}H_{30}NaO_5$ requires 397.1985).

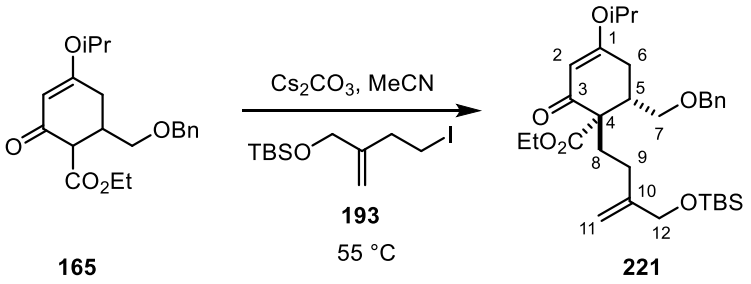
217 – (±)-Ethyl (4*S*,5*S*,8*R*,*Z*)-4-((benzyloxy)methyl)-2-methyl-6-oxobicyclo[4.2.2]dec-1-ene-5-carboxylate



214 **217**

214 (10 mg, 26 µmol) and pTSA (1.0 mg, 6 µmol) was heated to 110 °C in deuterated toluene (0.5 mL). After 3 h, ^{1}H-NMR showed full conversion to **217**; **IR** ν_{max}/cm^{-1} 2969, 2927, 1779, 1730; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 5H, C*H* arom.), 5.48 (d, *J* 7.0, 1H, *H*-1), 4.56 (d, *J* 11.7, 1H, -OC*H*$_2$Ph), 4.44 (d, *J* 11.8, 1H, -OC*H*$_2$Ph), 4.16 – 4.07 (m, 2H, -OC*H*$_2$CH$_3$), 3.72 (ddd, *J* 9.7, 3.1, 1.5, 1H, *H*-9), 3.12 (t, *J* 9.8, 1H, *H*-9), 2.84 (ddt, *J* 8.0, 7.0, 4.0, 1H, *H*-8), 2.80 – 2.71 (m, 2H, *H*-3,4), 2.57 (dd, *J* 15.1, 4.0, 1H, *H*-7), 2.43 – 2.33 (m, 3H, *H*-3,7,12), 2.29 – 2.00 (m, 3H, *H*$_2$-11 & *H*-12), 1.67 (s, 3H, *H*-1'), 1.20 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.8 (*C*-6), 173.5 (*C*-10), 138.8 (*C* arom.), 135.0 (*C*-2), 128.8 (*C*-1), 128.3 (*C*H arom.), 127.7 (*C*H arom.), 127.4 (*C*H arom.), 72.8 (-O*C*H$_2$Ph), 69.8 (*C*-9), 61.3 (-O*C*H$_2$CH$_3$), 60.2 (*C*-5), 45.9 (*C*-7), 43.7 (*C*-4), 31.4 (*C*-8), 29.4 (*C*-1'), 28.9 (*C*-12), 28.5 (*C*-3), 22.7 (*C*-11), 14.0 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 357.2064 [M+H]$^+$ 379.1881 [M+Na]$^+$ ($C_{22}H_{29}O_4$ requires 357.2060, $C_{22}H_{28}NaO_4$ requires 379.1880).

221 – (±)-Ethyl (4*S*,5*S*)-5-((benzyloxy)methyl)-4-(3-(((tert-butyldimethylsilyl)oxy)methyl)but-3-en-1-yl)-1-isopropoxy-3-oxocyclohex-2-ene-4-carboxylate



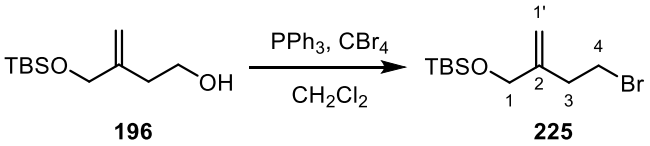
165 **221**

Cesium carbonate (8.05 g, 24.7 mmol) was added to a solution of **165** (4.28 g, 12.4 mmol) in dry acetonitrile (17 mL) at room temperature. After 1.5 h, **193** (2.24 g, 6.8 mmol) was added and the reaction mixture was heated to 55 °C. After 0.5 h a further portion of **193** (3.88 g, 11.7 mmol) was added and left at 55 °C. After a further 20 h, a final portion of **193** (0.72 g, 2.2 mmol) was added and the solution stirred for 16 h at 55 °C. The reaction mixture was cooled to room temperature and filtered by gravity filtration then the solvent removed under reduced pressure. The product was purified by column chromatography (10% ethyl acetate/petroleum

ether) to give **221** (3.96 g, 59% (91% BRSM), d.r. > 20:1) as a pale yellow oil; **IR** ν_{max}/cm^{-1} 3674, 2987, 2971, 2925, 2900, 1730, 1651, 1607, 1075, 1056; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H, C*H* arom.), 5.42 (s, 1H, *H*-2), 5.04 (q, *J* 1.8, 1H, *H*-11), 4.85 (q, *J* 1.5, 1H, *H*-11), 4.53 – 4.42 (m, 3H, -OC*H*$(CH_3)_2$ & -OCH_2Ph), 4.14 – 3.98 (m, 4H, *H*-12 & -OCH_2CH_3), 3.67 (dd, *J* 9.5, 3.4, 1H, *H*-7), 3.47 (dd, *J* 9.5, 7.9, 1H, *H*-7), 2.73 – 2.39 (m, 4H, *H*-5,6,8), 2.03 – 1.89 (m, 2H, *H*-8 & *H*-9), 1.71 (m, 1H, *H*-9), 1.31 (d, *J* 6.1, 3H, -OCH(CH_3)$_2$), 1.30 (d, *J* 6.1, 3H, -OCH(CH_3)$_2$), 1.14 (t, *J* 7.1, 3H, -OCH$_2$CH_3), 0.90 (s, 9H, -OSi$(CH_3)_2$(C(CH_3)$_3$), 0.06 (s, 6H, -OSi(CH_3)$_2$^{t}Bu); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 195.5 (*C*-3), 176.0 (*C*-1), 171.1 (*C*=O), 148.2 (*C*-10), 138.1 (*C* arom.), 128.5 (*C*H arom.), 127.8 (*C*H arom.), 127.7 (*C*H arom.), 108.8 (*C*-11), 103.1 (*C*-2), 73.4 (O*C*H$_2$Ph), 71.3 (-O*C*H$(CH_3)_2$), 70.1 (*C*-7), 65.8 (*C*-12), 61.2 (-O*C*H$_2$CH$_3$), 57.8 (*C*-4), 37.7 (*C*-5), 31.1 (*C*-6), 29.6 (*C*-8), 27.2 (*C*-9), 26.0 (-OSi$(CH_3)_2$(C(*C*H$_3$)$_3$), 21.6 (-OCH(*C*H$_3$)$_2$), 21.5 (-OCH(*C*H$_3$)$_2$), 18.5 (-OSi$(CH_3)_2$(*C*$(CH_3)_3$), 14.1 (-OCH$_2$*C*H$_3$), -5.3 (-OSi(*C*H$_3$)$_2$^{t}Bu); **HRMS** (ESI^+) 545.3291 $[M+H]^+$ 567.3095 $[M+Na]^+$ ($C_{31}H_{49}O_6Si$ requires 545.3220, $C_{31}H_{48}NaO_6Si$ requires 567.3112).

225 - 4-Bromo-2-methylenebutoxy-*tert*-butyl-dimethylsilane

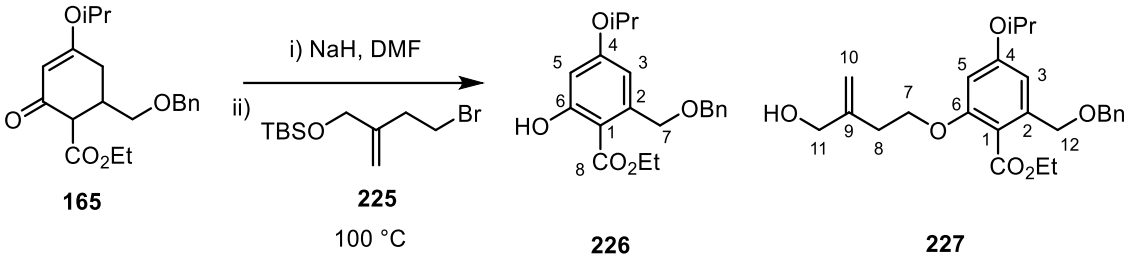
Molecular Weight: 279.2930



196 **225**

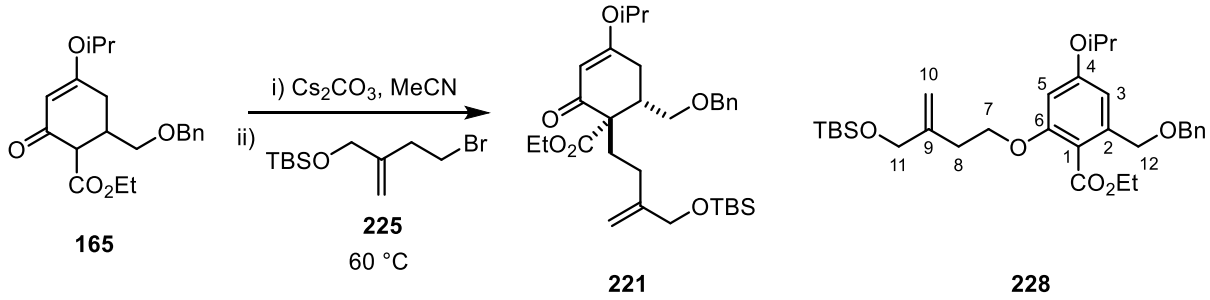
Carbon tetrabromide (1.61 g, 4.85 mmol) and triphenylphosphine (1.02 g, 3.88 mmol) were added to a solution of **196** (0.70 g, 3.23 mmol) in anhydrous DCM (21.0 mL) at room temperature. After 5 min, reaction completion was confirmed by TLC and the reaction mixture poured into a solution of saturated sodium hydrogen carbonate (20 mL) and then extracted with DCM (3 × 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was filtered through a silica plug eluting with 10% diethyl ether/hexane to give the pure product **225** as a colourless oil (0.90 g, >99%); **IR** ν_{max}/cm^{-1} 2995, 2929, 2886, 2856, 1252, 1083, 833, 774; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.12 (m, 1H, *H*-1'), 4.91 (m, 1H, *H*-1'), 4.14 – 4.06 (m, 2H, *H*-1), 3.49 (t, *J* 7.5, 2H, *H*-4), 2.61 (tdd, *J* 7.5, 1.3, 0.6, 2H, *H*-3), 0.91 (s, 9H, -OSi$(CH_3)_2$C(CH_3)$_3$), 0.07 (s, 6H, -OSi(CH_3)$_2$C$(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.7 (*C*-2), 111.7 (*C*-1'), 65.8 (*C*-1), 36.4 (*C*-3), 31.1 (*C*-4), 26.0 (-OSi$(CH_3)_2$*C*$(CH_3)_3$), 18.4 (-OSi$(CH_3)_2$C(*C*H$_3$)$_3$), -5.3 (-OSi(*C*H$_3$)$_2$C$(CH_3)_3$); **MS** (ESI^+) 279.1 $[M+H]^+$ 301.1 $[M+Na]^+$ ($C_{11}H_{24}OBr^{79}Si$ requires 279.1, $C_{11}H_{23}OBr^{79}Si$ requires 301.1).

226 and 227 - Ethyl 2-((benzyloxy)methyl)-6-hydroxy-4-isopropoxybenzoate and ethyl 2-((benzyloxy)methyl)-6-((2-(hydroxymethyl)allyl)oxy)-4-isopropoxybenzoate



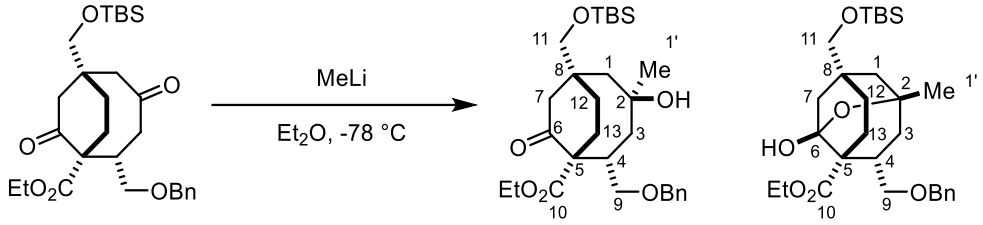
A solution of **165** (0.23 g, 0.65 mmol) in DMF (2.0 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 52 mg, 1.3 mmol) in DMF (3.0 mL) at room temperature and stirred for 10 min. A solution of **225** (0.20 g, 0.72 mmol) in DMF (2.0 mL) was added dropwise and stirred at room temperature for 2 h before heating to 100 °C for 24 h. The reaction was quenched with saturated ammonium chloride solution (10 mL) then extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (20% ethyl acetate/petroleum ether) to give **226** (65 mg, 29%) and **227** (37 mg, 13%) along with returned starting material **165** (45 mg, 20%); **226**: **IR** ν_{max}/cm^{-1} 2979, 2929, 1651, 1616, 1578; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.70 (s, 1H, -O*H*), 7.41 – 7.27 (m, 5H, C*H* arom.), 6.82 (dt, *J* 2.7, 1.0, 1H, *H*-3), 6.37 (d, *J* 2.7, 1H, *H*-5), 4.80 (t, *J* 1.0, 2H, *H*-7), 4.64 (s, 2H, -OC*H*$_2$Ph), 4.59 (h, *J* 6.1, 1H, -OC*H*$(CH_3)_2$), 4.35 (q, *J* 7.2, 2H, -OC*H*$_2$CH$_3$), 1.36 – 1.33 (m, 9H, -OCH(C*H*$_3)_2$, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0 (*C*-8), 165.4 (*C*-6), 163.1 (*C*-4), 143.5 (*C*-2), 138.3 (*C* arom.), 131.3 (*C*H arom.), 128.4 (*C*H arom.), 127.6 (*C*H arom.), 108.2 (*C*-3), 102.9 (*C*-1) 100.9 (*C*-5), 72.8 (-O*C*H$_2$Ph), 71.1 (*C*-7), 70.0 (-O*C*H$(CH_3)_2$), 61.3 (-O*C*H$_2$CH$_3$), 21.9 (-OCH(*C*H$_3)_2$, 14.2 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 345.1692 $[M+H]^+$ 367.1521 $[M+Na]^+$ ($C_{20}H_{25}O_5$ requires 345.1697, $C_{20}H_{24}NaO_5$ requires 367.1516); **227: IR** ν_{max}/cm^{-1} 3444, 2979, 2933, 1722, 1603, 1269, 1161, 1105; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H, C*H* arom.), 6.58 (d, *J* 2.2, 1H, *H*-3), 6.39 (d, *J* 2.2, 1H, *H*-5), 5.10 (s, 1H, *H*-10), 4.96 (s, 1H, *H*-10), 4.57 (s, 2H, PhC*H*$_2$), 4.50 (s, 2H, *H*-12), 4.43 (h, *J* 6.1, 1H, -OC*H*$(CH_3)_2$), 4.27 (q, *J* 7.1, 2H, -OC*H*$_2$CH$_3$), 4.13 (s, 2H, *H*-11), 4.10 (t, *J* 6.2, 2H, *H*-7), 2.57 (t, *J* 6.2, 2H, *H*-8), 1.61 (s, 1H, O*H*), 1.33 (d, *J* 6.1, 6H, -OCH(C*H*$_3)_2$), 1.29 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7 (*C*=O), 160.0 (*C*-4), 157.7 (*C*-6), 146.1 (*C*-9), 139.2 (*C*-2), 138.1 (*C* arom.), 128.4 (*C*H arom.), 127.8 (*C*H arom.), 127.6 (*C*H arom.), 115.1 (*C*-1), 112.4 (*C*-10), 106.5 (*C*-3), 100.5 (*C*-5), 72.3 (Ph*C*H$_2$), 71.1 (-O*C*H$(CH_3)_2$), 70.1 (*C*-12), 68.1 (*C*-7), 66.1 (*C*-11), 61.1 (-O*C*H$_2$CH$_3$), 32.8 (*C*-8), 22.0 (-OCH(*C*H$_3)_2$), 14.2 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 451.2105 $[M+Na]^+$ ($C_{25}H_{32}NaO_6$ requires 451.2091).

228 - Ethyl 2-((benzyloxy)methyl)-6-((3-(((*tert*-butyldimethylsilyl)oxy)methyl)but-3-en-1-yl)oxy)-4-isopropoxybenzoate



165 (0.50 g, 1.44 mmol) was dissolved in acetonitrile (1.0 mL) and cesium carbonate (0.94 g, 2.88 mmol) added. After 45 min, a solution of **225** (0.60 g, 2.16 mmol) in acetonitrile (1.0 mL) was added and the solution heated to 60 °C. After 65 h, the resulting suspension was filtered by gravity filtration and the filtrate concentrated under reduced pressure. The product was purified by column chromatography (10 % ethyl acetate/petroleum ether) to give the desired product **221** (85 mg, 11%) recovered starting material **165** (150 mg, 30%) and **228** (39 mg, 5%) **228**; **IR** ν_{max}/cm^{-1} 2929, 2856, 1721, 1654, 1602, 1099; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H, C*H* arom.), 6.58 (d, *J* 2.2, 1H, *H*-3), 6.38 (d, *J* 2.2, 1H, *H*-5), 5.12 (d, *J* 1.9, 1H, *H*-10), 4.92 (d, *J* 1.9, 1H, *H*-10), 4.57 (s, 2H, *H*-12), 4.51 (s, 2H, PhCH_2), 4.25 (q, *J* 7.1, 2H, -OCH_2CH$_3$), 4.10 (s, 2H, *H*-7), 4.07 (t, *J* 6.9, 2H, *H*-7), 2.49 (t, *J* 6.9, 2H, *H*-8), 1.32 (d, *J* 6.0, 6H, -CH(CH_3)$_2$), 1.28 (t, *J* 7.1, 3H, -OCH$_2$CH_3), 0.91 (s, 9H, -OSi(CH$_3$)$_2$C(CH_3)$_3$), 0.07 (s, 6H, -OSi(CH_3)$_2$C(CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7 (*C*=O), 159.9 (*C*-4), 157.7 (*C*-6), 144.9 (*C*-9), 139.0 (*C* arom.), 138.2 (*C*-2), 128.3 (*C*H arom.), 127.7 (*C*H arom.), 127.6 (*C*H arom.), 115.5 (*C*-1), 111.0 (*C*-10), 106.4 (*C*-3), 100.5 (*C*-5), 72.3 (Ph*C*H$_2$), 70.0 (*C*-12), 70.0 (-O*C*H(CH$_3$)$_2$), 67.6 (*C*-7), 66.1 (*C*-11), 60.9 (-O*C*H$_2$CH$_3$), 32.4 (*C*-8), 25.9 (-OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 22.0 (-OCH(*C*H$_3$)$_2$), 18.4 (-OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 14.2 (-OCH$_2$*C*H$_3$), -5.4 (-OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$); **HRMS** (ESI$^+$) 565.2941 [M+Na]$^+$ ($C_{31}H_{46}NaO_6Si$ requires 565.2956). Data for desired product **221** has been provided in a previous procedure.

230 and 231 – (±)-Ethyl (2*S*,4*S*,5*S*,8*R*)-4-((benzyloxy)methyl)-8-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-hydroxy-2-methyl-6-oxobicyclo[4.2.2]decane-5-carboxylate and (±)-Ethyl (2*S*,4*S*,5*S*,6*S*,8*R*)-4-((benzyloxy)methyl)-8-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-2-methylhexahydro-2H-2,8-methanochromene-5(5H)-carboxylate

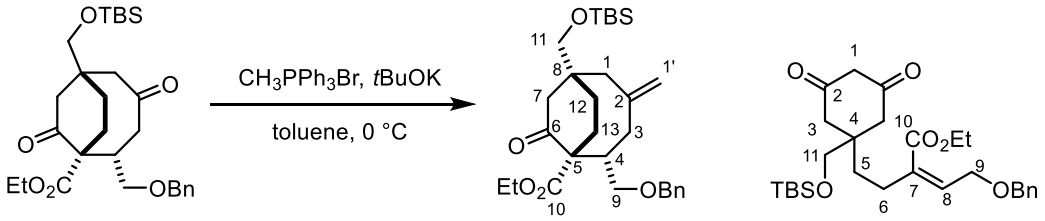


204 **230** **231**

204 (33.4 mg, 0.066 mmol) was dissolved in THF (0.5 mL) and cooled to -78 °C. Methyl lithium (41 µL, 1.6 M in diethyl ether, 0.066 mmol) was added and the solution slowly warmed to 0 °C over 5 h. The reaction was then quenched with saturated aqueous ammonium chloride solution (3 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (20% ethyl acetate/petroleum ether) to give **230** (5.5 mg, 18%) as a colourless oil and **231** (3.9 mg, 13%) also as a colourless oil. **230: IR** ν_{max}/cm^{-1} 3675 (w), 3477 (br), 2953, 2928, 1736, 1709, 1077; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H, C*H* arom.), 4.51 – 4.44 (m, 2H, -OC*H*$_2$Ph), 4.16 – 4.04 (m, 2H, -OC*H*$_2$CH$_3$), 3.74 (ddd, *J* 9.6, 3.0, 1.3, 1H, *H*-9), 3.24 – 3.12 (m, 3H, *H*-9,11), 2.69 (m, 1H, *H*-4), 2.61 (m, 1H, *H*-13), 2.50 (d, *J* 17.2, 1H, *H*-7), 2.30 – 2.04 (m, 4H, *H*-3,7,12,13), 1.82 – 1.59 (m, 3H, *H*-1,3,12), 1.37 (m, 1H, *H*-1), 1.24 (s, 3H, *H*-1'), 1.22 – 1.17 (m, 3H, -OCH$_2$C*H*$_3$), 0.89 (s, 9H, -OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.04 (s, 6H, -OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.8 (*C*-6), 173.0 (*C*-10), 138.6 (*C* arom.), 128.3 (*C*H arom.), 127.7 (*C*H arom.), 127.5 (*C*H arom.), 73.8 (*C*-11), 72.8 (-O*C*H$_2$Ph), 72.0 (*C*-9), 71.5 (*C*-2), 61.0 (-O*C*H$_2$CH$_3$), 58.7 (*C*-5), 49.8 (*C*-1), 49.2 (*C*-7), 42.8 (*C*-4), 39.9 (*C*-3), 38.7 (*C*-8), 37.0 (*C*-1'), 31.2 (*C*-13), 25.9 (-OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 24.6 (*C*-12), 18.3 (-OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 13.9 (-OCH$_2$*C*H$_3$), -5.5 (-OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$); **HRMS** (ESI$^+$) 541.2952 [M+Na]$^+$ ($C_{29}H_{46}NaO_6Si$ requires 541.2956); **231: IR** ν_{max}/cm^{-1} 3669 (w), 3403 (br), 2928, 1732, 1694, 1251, 1101; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H, C*H* arom.), 4.47 (d, *J* 11.8, 1H, -OC*H*$_2$Ph), 4.42 (d, *J* 11.8, 1H, -OC*H*$_2$Ph), 4.10 (dq, *J* 10.8, 7.1, 1H, -OC*H*$_2$CH$_3$), 3.99 (dq, *J* 10.8, 7.2, 1H, -OC*H*$_2$CH$_3$), 3.72 (dd, *J* 9.4, 7.1, 1H, *H*-9), 3.66 (dd, *J* 9.4, 5.0, 1H, *H*-9), 3.19 (s, 2H, *H*-11), 2.29 (m, 1H, *H*-4), 2.07 (dt, *J* 14.8, 7.4, 1H, *H*-3), 2.03 – 1.90 (m, 3H, *H*-3,13), 1.83 – 1.72 (m, 2H, *H*-7,12), 1.67 (m, 1H, *H*-12), 1.36 – 1.07 (m, 3H, *H*-1,7), 1.25 (s, 3H, *H*-1'), 1.18 (t, *J* 7.2, 3H, -OCH$_2$C*H*$_3$), 0.88 (s, 9H, -OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.01 (s, 6H, -OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.3

(*C*-10), 138.5 (*C* arom.), 128.3 (*C*H arom.), 127.9 (*C*H arom.), 127.5 (*C*H arom.), 96.0 (*C*-6), 74.5 (*C*-9), 73.0 (-O*C*H$_2$Ph), 72.6 (*C*-11), 71.6 (*C*-2), 61.4 (-O*C*H$_2$CH$_3$), 49.6 (*C*-5), 46.4 (*C*-1), 43.4 (*C*-4), 40.1 (*C*-7), 36.3 (*C*-8), 34.5 (*C*-1'), 34.1 (*C*-3), 32.9 (*C*-13), 28.2 (*C*-12), 25.9 (-OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 18.3 (-OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 13.8 (-OCH$_2$*C*H$_3$), -5.5 (-OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$); **HRMS** (ESI$^+$) 541.2952 [M+Na]$^+$ ($C_{29}H_{46}NaO_6Si$ requires 541.2956).

235 and 236 – (±)-Ethyl (4*S*,5*S*,8*R*)-4-((benzyloxy)methyl)-8-(((tert-butyldimethylsilyl)oxy)methyl)2-methylene-6-oxobicyclo[4.2.2]decane-5-carboxylate and (±)-Ethyl (*Z*)-4-(benzyloxy)-2-(2-(1-(((tert-butyldimethylsilyl)oxy)methyl)-3,5-dioxocyclohexyl)ethyl)but-2-enoate

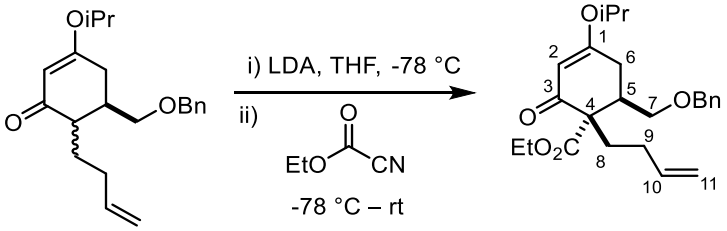


204 **235** **236**

Potassium *tert*-butoxide (0.11 g, 0.95 mmol) was added to a suspension of methyltriphenylphosphonium bromide (0.40 g, 1.11 mmol) in toluene (7.0 mL) and warmed to 40 °C. After 1 h, the resulting thick yellow solution was cooled to room temperature and diluted with THF (7.0 mL) and then added to a solution of **204** (0.20 g 0.40 mmol) in toluene (7.0 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and then at room temperature for 30 min before quenching with saturated aqueous sodium chloride (10 mL). The solution was extracted with diethyl ether (3 × 10 mL) and the combined organic extracts dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by column chromatography (10% ethyl acetate/petroleum ether) to give the product **235** (0.12 g, 61%) as a colourless solid and **236** (30 mg, 15%) as a colourless oil. **235: m.p.** (ethyl acetate) 76-77 °C; **IR** ν_{max}/cm^{-1} 3675, 2987, 2901, 1066; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H, C*H* arom.), 4.91 (s, 1H, *H*-1'), 4.59 (d, *J* 12.0, 1H, -OC*H*$_2$Ph), 4.57 (s, 1H, *H*-1'), 4.45 (d, *J* 12.0, 1H, -OC*H*$_2$Ph), 4.19 – 4.04 (m, 2H, -OC*H*$_2$CH$_3$), 3.65 (dd, *J* 9.9, 2.5, 1H, *H*-9), 3.48 (t, *J* 9.9, 1H, *H*-9), 3.26 (d, *J* 9.4, 1H, *H*-11), 3.20 (d, *J* 9.4, 1H, *H*-11), 2.80 (dd, *J* 14.0, 2.5, 1H, *H*-3), 2.66 (dddd, *J* 9.9, 5.6, 2.9, 2.5, 1H, *H*-4), 2.46 (dd, *J* 16.6, 2.0, 1H, *H*-7), 2.32 (dd, *J* 14.0, 5.6, 1H, *H*-3), 2.22 (ddd, *J* 14.7, 10.9, 9.5, 1H, *H*-13), 2.19 – 2.08 (m, 3H, *H*-1,7,13), 2.08 – 2.00 (m, 2H, *H*-1,12), 1.84 (dtd, *J* 14.5, 9.5, 2.0, 1H, *H*-12), 1.19 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$), 0.89 (s, 9H, -OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.05 (s, 6H, -OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.8 (*C*-6), 173.5 (*C*-10), 141.4 (*C*-2), 138.8 (*C* arom.), 128.3 (*C*H arom.), 127.8 (*C*H arom.), 127.4 (*C*H arom.), 120.2 (*C*-1'), 72.7 (-O*C*H$_2$Ph), 72.3 (*C*-11), 68.7 (*C*-9), 61.2 (-O*C*H$_2$CH$_3$),

58.9 (*C*-5), 46.6 (*C*-7), 44.0 (*C*-4), 39.1 (*C*-8), 31.2 (*C*-3), 31.0 (*C*-13), 27.4 (*C*-12), 25.9 (-OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 18.3 (-OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 13.9 (-OCH$_2$*C*H$_3$), -5.5 (-OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$); **HRMS** (ESI$^+$) 501.3047 [M+H]$^+$ 523.2854 [M+Na]$^+$ (C$_{29}$H$_{45}$O$_5$Si requires 501.3031, C$_{29}$H$_{44}$NaO$_5$Si requires 523.2850). **236: IR** ν_{max}/cm^{-1} 3675, 2956, 2928, 2901, 1709, 1075; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.39 – 7.27 (m, 5H, C*H* arom.), 6.16 (tt, *J* 4.8, 1.2, 1H, *H*-8), 4.53 (s, 2H, *H*-11), 4.46 (dt, *J* 4.8, 1.2, 2H, *H*-9), 4.18 (q, *J* 7.2, 2H, -OC*H*$_2$CH$_3$), 3.48 (s, 2H, *H*-11), 3.28 (dt, *J* 18.0, 1.9, 1H, *H*-1), 3.19 (dt, *J* 18.0, 0.9, 1H, *H*-1), 2.55 (dd, *J* 15.5, 0.9, 1H, *H*-3), 2.46 (d, *J* 15.5, 2H, *H*-3), 2.30 – 2.18 (m, 2H, *H*-6), 1.48 – 1.39 (m, 2H, *H*-5), 1.28 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$), 0.83 (s, 9H, -OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.00 (s, 6H, -OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ 203.1 (*C*-2), 166.5 (*C*-10), 142.4 (*C*-8), 137.9 (*C* arom.), 130.8 (*C*-7), 128.5 (*C*H arom.), 127.8 (*C*H arom.), 127.8 (*C*H arom.), 72.9 (-O*C*H$_2$Ph), 71.4 (*C*-11), 68.9 (*C*-9), 60.7 (-O*C*H$_2$CH$_3$), 56.5 (*C*-1), 48.9 (*C*-3), 40.4 (*C*-4), 37.3 (*C*-5), 27.8 (*C*-6), 25.9 (-OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 18.5 (-OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), 14.3 (-OCH$_2$*C*H$_3$), -6.1 (-OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$); **HRMS** (ESI$^+$) 503.2838 [M+H]$^+$ 525.2661 [M+Na]$^+$ (C$_{28}$H$_{43}$O$_6$Si requires 503.2823, C$_{28}$H$_{42}$NaO$_6$Si requires 525.2643).

4-*epi*-167 – (±)-Ethyl (4*S*,5*R*)5-((benzyloxy)methyl)-4-(but-3-en-1-yl)-1-isopropoxy-3-oxocyclohex-2-ene-4-carboxylate

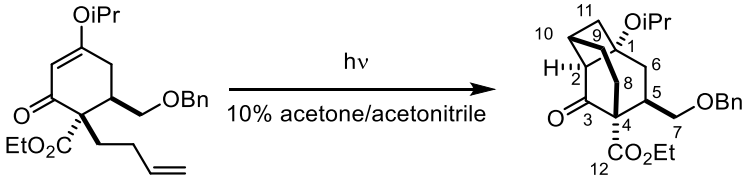


238 **4-*epi*-167**

A solution of **238** (0.34 g, 1.03 mmol) in THF (1 mL) was added to a freshly prepared solution of LDA (1.55 mmol) in THF (5 mL) at -78 °C. After 2 h, ethyl cyanoformate (0.14 mL, 1.55 mmol) was added dropwise over 5 min and the reaction warmed to room temperature. After 16 h, the reaction was quenched with water (2 mL) then aqueous hydrochloric acid (3.0 M, 2 mL) and left to stir for 30 min. The organics were extracted with diethyl ether (3 × 10 mL) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography (20% ethyl acetate/petroleum ether) to give the product **4-*epi*-167** (0.20 g, 48%) as a colourless oil; **IR** ν_{max}/cm^{-1} 2979, 2933, 2867, 1732, 1650, 1603, 1209, 1186, 1103; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.38 – 7.22 (m, 5H, C*H* arom.), 5.77 (ddt, *J* 16.6, 10.1, 6.2, 1H, *H*-10), 5.32 (d, *J* 1.0, 1H, *H*-2), 5.04 – 4.86 (m, 2H, *H*-11), 4.49 – 4.36 (m, 3H, C*H*$_2$Ph & C*H*(CH$_3$)$_2$), 4.19 – 4.10 (m,

2H, -OC*H*$_2$CH$_3$), 3.44 – 3.29 (m, 2H, *H*-7), 3.05 (ddt, *J* 9.1, 7.8, 5.4, 1H, *H*-5), 2.60 (dd, *J* 18.3, 5.4, 1H, *H*-6), 2.41 (ddd, *J* 18.3, 9.1, 1.0, 1H, *H*-6), 2.27 (m, 1H, *H*-9), 1.89 – 1.71 (m, 3H, *H*-9 & *H*$_2$-8), 1.28 (d, *J* 6.1, 6H, -CH(C*H*$_3$)$_2$), 1.20 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 196.3 (*C*-3), 174.1 (*C*-1), 171.9 (*C*-12), 138.5 (*C*-10), 137.9 (*C* arom.), 128.4 (*C*H arom.), 127.7 (*C*H arom.), 127.6 (*C*H arom.), 114.6 (*C*-11), 102.0 (*C*-2), 73.2 (*C*H$_2$Ph), 71.3 (-O*C*H(CH$_3$)$_2$), 69.5 (*C*-7), 61.1 (-O*C*H$_2$CH$_3$), 58.4 (*C*-4), 39.1 (*C*-5), 29.9 (*C*-6), 29.2 (*C*-9), 27.8 (*C*-8), 21.5 (-OCH(*C*H$_3$)$_2$), 21.4 (-OCH(*C*H$_3$)$_2$), 14.0 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 401.2326 [M+H]$^+$ 423.2143 [M+Na]$^+$ (C$_{24}$H$_{33}$O$_5$ requires 401.2323, C$_{24}$H$_{32}$NaO$_5$ requires 423.2142).

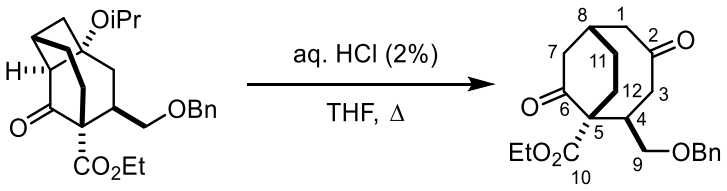
5-*epi*-200 – (±)-Ethyl (1*R*,2*S*,4*S*,5*R*,10*S*)-5-((benzyloxy)methyl)-1-isopropoxy-3-oxotricyclo[4.2.2.0^{1,2}]-decane-4-carboxylate



4-*epi*-167 **5-*epi*-200**

4-*epi*-167 (190 mg, 0.47 mmol) was dissolved in acetone (15 mL) and acetonitrile (135 mL) and irradiated with a medium pressure Hg lamp. After 2 h, the reaction was shown to be complete by TLC and irradiation was stopped and the solvent removed under reduced pressure. The product was purified by column chromatography (20% ethyl acetate/petroleum ether) to give **5-*epi*-200** (95 mg, 50%) as a colourless oil; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.36 – 7.25 (m, 5H, C*H* arom.), 4.47 (d, *J* 12.1, 1H, PhC*H*$_2$), 4.43 (d, *J* 12.1, 1H, PhC*H*$_2$), 4.16 (q, *J* 7.1, 2H, -OC*H*$_2$CH$_3$), 3.65 (h, *J* 6.2, 1H, -C*H*(CH$_3$)$_2$), 3.49 (d, *J* 5.1, 1H, *H*-7), 3.48 (d, *J* 6.6, 1H, *H*-7), 2.96 (d, *J* 10.0, 1H, *H*-2), 2.94 – 2.79 (m, 2H, *H*-5 & *H*-10), 2.64 – 2.53 (m, 2H, *H*-6 & *H*-11), 2.48 – 2.35 (m, 2H, *H*-6 & *H*-8), 2.20 (dd, *J* 16.1, 11.7 1H, *H*-8), 1.93 (dd, *J* 12.3, 2.6, 1H, *H*-11), 1.81 – 1.61 (m, 2H, *H*-9), 1.21 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$), 1.14 (t, *J* 6.2, 6H, -CH(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 211.1 (*C*-3), 171.9 (*C*-12), 138.2 (*C* arom.), 128.4 (*C*H arom.), 127.7 (*C*H arom.), 127.5 (*C*H arom.), 79.0 (*C*-1), 73.2 (Ph*C*H$_2$), 71.9 (*C*-7), 66.4 (-*C*H(CH$_3$)$_2$), 61.3 (-O*C*H$_2$CH$_3$), 59.8 (*C*-4), 52.2 (*C*-2), 41.8 (*C*-5), 37.8 (*C*-8), 31.1 (*C*-10), 27.7 (*C*-6), 25.3 (*C*-9), 24.8 (-CH(*C*H$_3$)$_2$), 24.7 (-CH(*C*H$_3$)$_2$), 14.1 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 423.2153 [M+Na]$^+$ (C$_{24}$H$_{32}$NaO$_5$ requires 423.2142).

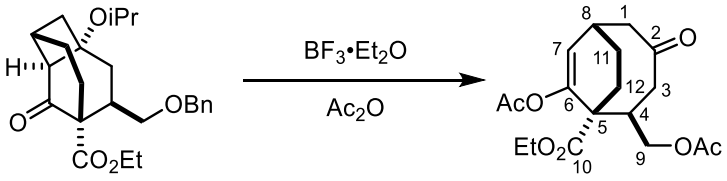
4-*epi*-201 – (±)-Ethyl-(4*R*,5*S*,8*S*)4-((benzyloxy)methyl)-2,6-dioxobicyclo[4.2.2]decane-5-carboxylate



5-*epi*-200 **4-*epi*-201**

5-*epi*-200 (35 mg, 0.087 mmol) was dissolved in THF (0.6 mL) and aqueous hydrochloric acid (2%, 0.3 mL) and heated at reflux. After 1.5 h, the reaction was quenched with water and the solution extracted with DCM (3 × 5 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to give the product **4-*epi*-201** (23 mg, 75%) as a colourless oil; **IR** ν_{max}/cm^{-1} 2976, 2937, 2900, 1739, 1709, 1696, 749; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H, C*H* arom.), 4.55 (d, *J* 12.2, 1H, -OC*H*$_2$Ph), 4.52 (d, *J* 12.2, 1H, -OC*H*$_2$Ph), 4.12 (m, 2H, OC*H*$_2$CH$_3$), 3.57 (d, *J* 6.1, 2H, *H*-9), 3.05 (p, *J* 6.1, 1H, *H*-4), 2.88 – 2.78 (m, 2H, *H*-3,7), 2.71 – 2.60 (m, 3H, *H*-1,7,8), 2.59 – 2.42 (m, 3H, *H*-1,3,12), 2.12 (m, 1H, *H*-11), 1.93 – 1.85 (m, 2H, *H*-11,12), 1.20 (t, *J* 7.1, 3H, -OCH$_2$C*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 212.0 (*C*-2), 208.8 (*C*-6), 170.9 (*C*-10), 138.3 (*C* arom.), 128.3 (*C*H arom.), 127.6 (*C*H arom.), 127.5 (*C*H arom.), 73.0 (-O*C*H$_2$Ph), 69.4 (C-9), 61.7 (-O*C*H$_2$CH$_3$), 60.8 (*C*-5), 52.5 (*C*-1), 44.3 (*C*-7), 42.6 (*C*-4), 41.1 (*C*-3), 28.0 (*C*-8), 24.4 (*C*-11), 23.1 (*C*-12), 14.1 (-OCH$_2$*C*H$_3$); **HRMS** (ESI^+) 381.1668 $[M+Na]^+$ ($C_{21}H_{26}NaO_5$ requires 381.1672).

4-*epi*-202 – (±)-Ethyl (4*R*,5*S*,8*S*)-6-acetoxy-4-(acetoxymethyl)-2-oxobicyclo[4.2.2]dec-7-ene-5-carboxylate

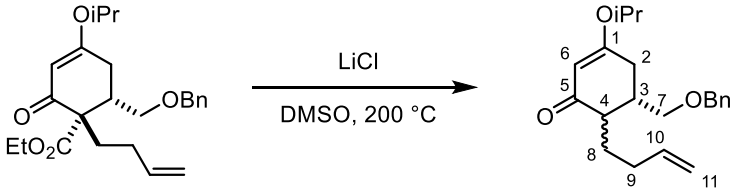


5-*epi*-200 **4-*epi*-202**

5-*epi*-200 (35 mg, 0.080 mmol) was dissolved in acetic anhydride (0.5 mL) and borontrifluoride diethyletherate (10 µL, 0.080 mmol) added dropwise. After 10 min, the reaction was quenched with water (1 mL) and extracted with DCM (3 × 5 mL). The organic layers were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was dissolved by column chromatography (35% ethyl acetate/petroleum ether) to give the diacetate **4-*epi*-202** (11 mg, 36%) as a colourless oil; **IR** ν_{max}/cm^{-1} 2981, 2937, 1763, 1733, 1691, 1213, 1199; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.15 (d, *J* 8.1, 1H, *H*-7), 4.27 – 4.04 (m, 4H, *H*$_2$-9 & -OC*H*$_2$CH$_3$), 3.21 (dd, *J* 11.8, 5.7, 1H, *H*-3), 2.84 (m, 1H, *H*-8), 2.77 (m, 1H,

H-4), 2.71 (dd, *J* 13.6, 3.4, 1H, *H*-1), 2.57 (dd, *J* 13.6, 4.9, 1H, *H*-1), 2.40 (ddd, *J* 11.8, 3.3, 1.2, 1H, *H*-3), 2.35 (m, 1H, *H*-12), 2.10 (s, 3H, C*H*$_3$), 2.06 (s, 3H, C*H*$_3$), 1.84 (m, 1H, *H*-11), 1.71 – 1.51 (m, 3H, *H*-11,12); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 213.2 (*C*-2), 172.6 (*C*-10), 170.8 (*C*=O), 168.8 (*C*=O), 146.7 (*C*-6), 121.1 (*C*-7), 62.4 (*C*-9), 61.7 (-O*C*H$_2$CH$_3$), 51.4 (*C*-1), 51.1 (*C*-5), 40.2 (*C*-3), 39.4 (*C*-4), 30.7 (*C*-8), 25.1 (*C*-11), 24.7 (*C*-12), 21.0 (*C*H$_3$), 20.9 (*C*H$_3$), 14.0 (-OCH$_2$*C*H$_3$); **HRMS** (ESI$^+$) 375.1426 $[M+Na]^+$ ($C_{18}H_{24}NaO_7$ requires 375.1414).

238 – (±)-5-((Benzyloxy)methyl)-4-(but-3-en-1-yl)-1-isopropoxycyclohex-6-en-5-one



167 **238**

167 (0.77 g, 1.92 mmol) and lithium chloride (0.20 g, 4.81 mmol) were dissolved in DMSO (5 mL) and heated to 200 °C. After 4 h, the reaction mixture was cooled to room temperature and diluted with DCM (10 mL). The organics were extracted with DCM (3 × 10 mL) and the combined organic layers washed with water (3 × 25 mL), dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography to give the product **238** (0.38 g, 60%, d.r. 3:1) as a colourless oil; **IR** ν_{max}/cm^{-1} 2979, 2927, 1650, 1604, 1382, 1212, 1106, 905, 732; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 5H, C*H* arom.), 5.75 (ddt, *J* 16.8, 10.0, 6.6, 1H, *H*-10), 5.20 (d, *J* 3.4, 1H, *H*-6), 5.02 – 4.86 (m, 2H, *H*-11), 4.47 (d, *J* 12.1, 1H, PhC*H*$_2$), 4.41 (d, *J* 12.1, 1H, PhC*H*$_2$), 4.35 (h, *J* 6.1, 1H, -C*H*(CH$_3$)$_2$), 3.39 (d, *J* 5.9, 2H, *H*-7), 2.50 (dd, *J* 17.9, 5.0, 1H, *H*-2), 2.40 (dd, *J* 17.9, 5.7, 1H, *H*-2), 2.30 – 2.18 (m, 2H, *H*-3,4), 2.10 – 1.98 (m, 2H, *H*-9), 1.80 – 1.57 (m, 2H, *H*-8), 1.23 (d, *J* 6.1, 3H, -CH(C*H*$_3$)$_2$), 1.22 (d, *J* 6.1, 3H, -CH(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.2 (*C*-5), 174.0 (*C*-1), 138.4 (*C* arom.), 128.5 (*C*H arom.), 127.8 (*C*H arom.), 127.6 (*C*H arom.), 114.9 (*C*-11), 101.9 (*C*-6), 73.3 (Ph*C*H$_2$), 71.7 (*C*-7), 71.0 (-*C*H(CH$_3$)$_2$), 46.8 (*C*-4), 36.8 (*C*-3), 31.0 (*C*-9), 30.3 (*C*-2), 28.2 (*C*-8), 21.6 (-CH(*C*H$_3$)$_2$); **HRMS** (ESI$^+$) 351.1944 $[M+Na]^+$ ($C_{21}H_{28}NaO_3$ requires 351.1931).

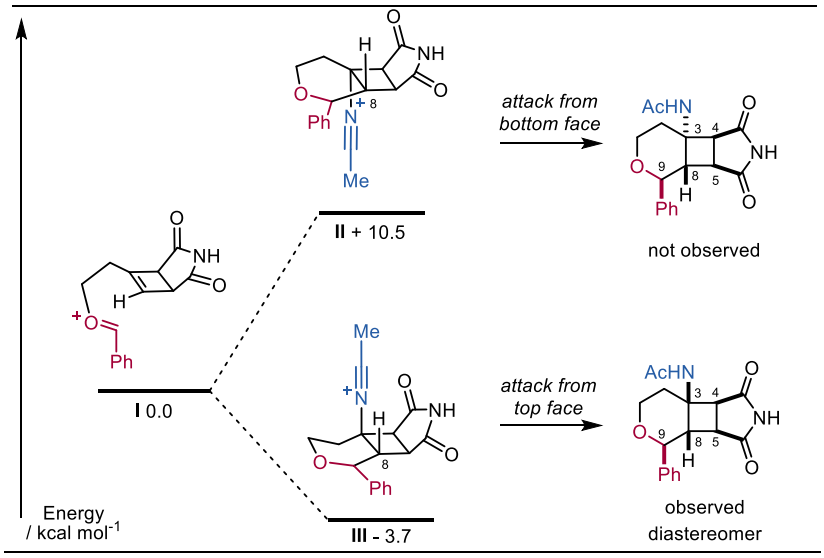
4.5. Computational Modelling

Conformational searches were carried out using Spartan using the MMFF forcefield extracting a selection of the lowest energy conformers. Geometries were then fully optimised in Gaussian091 using the B3LYP functional and the 6-31+G(d) basis set as implemented in Gaussian. Frequencies at the same level of theory were calculated for all geometries, both to confirm them as ground states and to obtain Gibbs free energy corrections with default settings, i.e. at 298.15 K. In some cases calculations were repeated with a continuum dielectric model of solvation.[186,214–218]

4.5.1. Raw Data for Chapter 2

Key energy differences have been summarised in the table below. Generally, moving to Gibbs Free energy values gave an overall increase in energy in all intermediates relative to A due to entropic factors. Solvation led to a stabilisation of all cationic intermediates. Despite the changes in relative energies, the effect on the energy difference between intermediates **II** and **III** was only small and all cases showed a preference for the reaction intermediate (**III**) in line with our experimental data. For clarity, we have focussed on the relative potential energies in the gas phase here.

Table 12 - Differences between the two possible modes of attack (i.e. intermediates **II** and **III** are shown in the table below).



/ kcal mol^{-1}	Gas phase		Solvated	
	Potential Energy	Gibbs Free Energy	Potential Energy	Gibbs Free Energy
ΔE_{III}-E_I	-3.75	4.98	-55.70	-46.83
ΔE_{II}-E_I	10.53	19.14	-45.96	-36.43
ΔE_{III}-E_{II}	-14.27	-14.16	-9.74	-10.40

4.5.1.1. Cartesian Coordinates

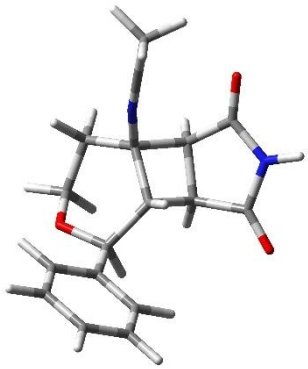


Table 12 - I

Gas phase:

Potential energy / a.u. = -992.9407

Free energy / a.u. = -992.6745

Solvated (acetonitrile):

Potential energy / a.u. = -993.0235

Free energy / a.u. = -992.7571

C	0.50457563	-1.35421502	-2.62057027
O	1.54370853	-1.17338976	-1.64967319
C	2.00857799	-0.02222173	-1.42039329
C	-0.14409432	1.04649804	-0.53030543
C	-0.94506939	0.27321672	-1.39764355
C	-0.86406718	-1.15907911	-1.94212867
C	-0.73723332	2.33625772	-1.13612703
C	-1.82367089	1.51305889	-1.64905700
C	-1.33121455	3.42473228	-0.24929682
N	-2.74820808	3.05894202	0.04599448
C	-2.85218192	1.67109844	-0.51352496
N	-2.61956437	-2.83040021	0.54397505
C	-3.51187780	-3.52314138	0.65251519
C	-4.61574301	-4.38357630	0.84496841
O	-3.63870137	0.77519801	-0.10208776
O	-0.72044537	4.44334854	0.17664369
C	3.14018514	0.15828301	-0.38949414
C	3.64084252	1.43947430	-0.11197721
C	4.67272006	1.60061797	0.82669677
C	5.19765982	0.48345335	1.48587443
C	4.69662993	-0.79292840	1.21050310
C	3.66681711	-0.95775307	0.27318175
H	0.57404416	0.82818648	0.23350303
H	0.56246317	-2.34281315	-3.02837540
H	0.62462984	-0.63574266	-3.40809980
H	1.61467408	0.83101698	-1.93698216
H	-0.97020277	-1.85971069	-1.13918907
H	-1.64742642	-1.31822295	-2.65296000
H	-0.05048217	2.75759773	-1.83967223
H	-2.28636294	1.70295858	-2.59763737
H	-2.95578029	3.11771051	1.02235715
H	-4.42469185	-5.32473025	0.35649767
H	-4.75366517	-4.54044514	1.88680623
H	-5.50546223	-3.93930067	0.43133193
H	3.23772748	2.29208466	-0.61796932
H	5.05828445	2.57427344	1.03895778
H	5.98459788	0.60779828	2.20074412
H	5.10029890	-1.64299016	1.71773946
H	3.28534106	-1.93668453	0.06194388

Table 12 - II

Gas phase:

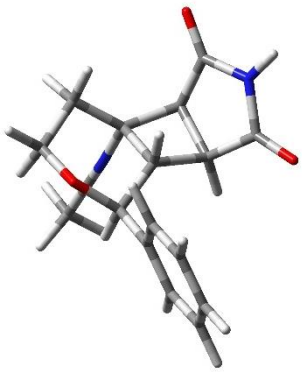
Potential energy / a.u. = -992.9179

Free energy / a.u. = -992.6519

Solvated (acetonitrile):

Potential energy / a.u. = -993.0079

Free energy / a.u. = -992.7405



C	0.888109	-1.800420	-2.088932
O	-0.442603	-1.446519	-1.721982
C	-0.687390	-1.094998	-0.345713
C	0.255794	0.088463	-0.115043
C	1.739578	-0.270323	-0.366638
C	1.952908	-0.700593	-1.816287
C	0.686183	0.969225	1.111834
C	2.106312	1.001000	0.464955
C	0.185692	2.409936	1.049439
N	1.053349	3.072180	0.160091
C	2.119560	2.324756	-0.321083
N	2.144007	-1.393019	0.487438
C	2.548963	-2.253494	1.136908
C	3.045587	-3.345745	1.952621
O	2.914377	2.646272	-1.171203
O	-0.760220	2.904089	1.605100
C	-2.148193	-0.762263	-0.163806
C	-2.787816	-1.094407	1.035556
C	-4.121187	-0.742481	1.244782
C	-4.826024	-0.062904	0.250324
C	-4.194352	0.262654	-0.951974
C	-2.858927	-0.080574	-1.159580
H	0.006010	0.787398	-0.920687
H	0.845736	-2.015411	-3.158908
H	1.182358	-2.732915	-1.578732
H	-0.420916	-1.939597	0.311382
H	1.788152	0.175957	-2.449048
H	2.961047	-1.076775	-2.020936
H	0.573947	0.525673	2.101627
H	3.003027	0.941059	1.087785
H	0.886106	4.026943	-0.142291
H	4.090427	-3.550598	1.693509
H	2.981327	-3.071193	3.011437
H	2.442097	-4.242317	1.771623
H	-2.246986	-1.636808	1.808915
H	-4.609944	-1.006423	2.177921
H	-5.866042	0.206524	0.408684
H	-4.743548	0.782003	-1.731833
H	-2.375504	0.154615	-2.102637

Table 12 - III

Gas phase:

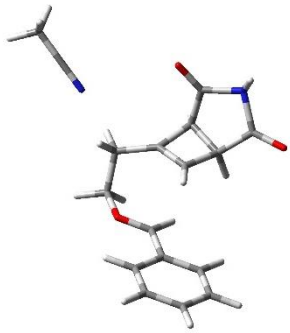
Potential energy / a.u. = -992.93471

Free energy / a.u. = -992.6824

Solvated (acetonitrile):

Potential energy / a.u. = -992.9347

Free energy / a.u. = -992.6824



C	0.142360	-1.285359	-2.752525
O	1.298920	-1.127159	-1.952878
C	1.296378	0.073573	-1.198153
C	-0.066198	0.283442	-0.457067
C	-1.200557	-0.797084	-0.658273
C	-1.011181	-1.755421	-1.859379
C	-1.060591	1.363614	-1.018560
C	-2.223518	0.367314	-0.864562
C	-1.356785	2.508342	-0.059334
N	-2.464947	2.093569	0.706269
C	-2.956465	0.839887	0.400813
N	-1.512806	-1.576360	0.517870
C	-1.944166	-2.078764	1.459830
C	-2.498182	-2.699765	2.644008
O	-3.780856	0.208985	1.032098
O	-0.756680	3.542153	0.083152
C	2.466241	0.066923	-0.232633
C	2.838199	1.272064	0.379564
C	3.888524	1.300463	1.295774
C	4.580068	0.125931	1.603020
C	4.215473	-1.073321	0.990341
C	3.159519	-1.106852	0.076471
H	0.121114	0.447919	0.606358
H	0.368145	-2.053750	-3.495607
H	-0.098615	-0.357059	-3.293168
H	1.410145	0.925469	-1.888626
H	-0.741088	-2.746666	-1.483287
H	-1.952123	-1.852530	-2.412494
H	-0.817235	1.723732	-2.019009
H	-2.936745	0.211811	-1.678582
H	-2.823859	2.645899	1.479083
H	-2.766506	-3.739508	2.427676
H	-1.766713	-2.670763	3.458953
H	-3.395804	-2.137523	2.928438
H	2.311971	2.193641	0.135086
H	4.174727	2.240347	1.758731
H	5.405088	0.149051	2.308996
H	4.758239	-1.986802	1.216705
H	2.887760	-2.035475	-0.413190

4.5.2. Raw Data for Chapter 3

176$_{ax}$

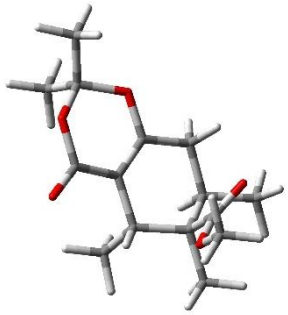
Gas phase:

Potential energy / a.u. = -960.699954302

Free energy / a.u. = -960.390916

C	0.58309	0.99648	-0.09149
C	-0.84640	0.46099	-0.15408
C	-1.14208	-0.85864	-0.01629
C	-0.13182	-1.95411	0.11564
C	1.26941	-1.48612	-0.32610
C	1.59560	-0.10809	0.36594
O	-2.43828	-1.34585	-0.03623
C	1.38105	-1.44314	-1.86406
C	1.59418	-0.29761	1.90849
C	-1.91372	1.37532	-0.57803
O	-3.22419	0.85033	-0.58765
C	-3.52095	-0.36100	0.17033
C	-4.76584	-0.96512	-0.44395
C	-3.63645	-0.04124	1.65777
O	-1.76093	2.51923	-1.01128
C	3.00214	0.30133	-0.07264
O	3.30435	1.24185	-0.81531
O	3.95890	-0.54727	0.44338
C	5.35530	-0.27310	0.07110
C	0.68053	2.27416	0.78032
H	0.87239	1.30000	-1.10611
H	-0.12151	-2.32095	1.15110
H	-0.46515	-2.79975	-0.49937
H	2.00609	-2.20719	0.04736
H	1.22922	-2.44707	-2.27713
H	0.63053	-0.78224	-2.31005
H	2.17961	-1.17846	2.18429
H	-4.59262	-1.15741	-1.50467
H	-5.01150	-1.90526	0.05720
H	-5.60306	-0.27025	-0.34080
H	-3.89358	-0.94705	2.21383
H	-2.69794	0.35988	2.04968
H	-4.42109	0.70506	1.80785
H	5.47599	-0.33595	-1.01250
H	5.64571	0.72425	0.40776
H	0.31196	2.10140	1.79741
H	0.57308	-0.41733	2.28290
H	1.71936	2.61294	0.83511
H	0.08620	3.07105	0.33117
H	2.03231	0.56563	2.41621
H	2.36683	-1.09499	-2.18941
H	5.93392	-1.04328	0.57715

176$_{eq}$



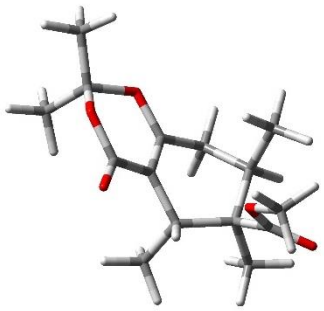
Gas phase:

Potential energy / a.u. = -960.702955909

Free energy / a.u. = -960.393960

C	-0.71760	-0.39269	1.27674
C	0.60120	-0.25195	0.53294
C	0.85228	0.78343	-0.30908
C	-0.13412	1.84298	-0.68096
C	-1.40930	1.82206	0.19422
C	-1.86996	0.36130	0.51145
O	2.05935	0.92679	-0.97033
C	-2.48890	2.73161	-0.42426
C	-3.17118	0.35732	1.35840
C	1.58126	-1.32557	0.68357
O	2.78871	-1.17251	-0.02930
C	3.21255	0.16468	-0.44315
C	4.16444	-0.02153	-1.60532
C	3.79824	0.91582	0.74857
O	1.40989	-2.37174	1.31448
C	-2.16536	-0.41527	-0.77825
O	-2.13415	0.01982	-1.93753
O	-2.52068	-1.71666	-0.51215
C	-2.82442	-2.57677	-1.66663
C	-0.55323	0.02589	2.75767
H	-0.97612	-1.45649	1.27580
H	0.35491	2.82331	-0.61097
H	-0.40607	1.70072	-1.73471
H	-1.14393	2.25083	1.17159
H	-2.07357	3.73047	-0.60639
H	-2.83956	2.33092	-1.37927
H	-4.03078	0.68461	0.76570
H	3.66170	-0.56885	-2.40520
H	4.48658	0.95232	-1.98361
H	5.03847	-0.59084	-1.27905
H	4.15139	1.90064	0.43061
H	3.05054	1.04714	1.53596
H	4.63782	0.34845	1.15883
H	-3.67511	-2.17518	-2.22117
H	-1.95684	-2.63707	-2.32663
H	-0.32326	1.09246	2.86313
H	-3.07251	1.03576	2.21130
H	-1.45087	-0.19606	3.34261
H	0.27326	-0.54328	3.19517
H	-3.38207	-0.64897	1.72946
H	-3.34734	2.85308	0.24360
H	-3.05697	-3.54729	-1.23371

176$_{TS}$



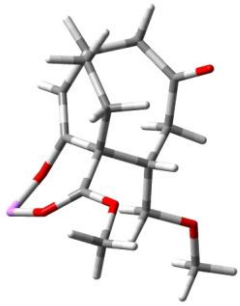
Gas phase:

Potential energy / a.u. = -960.687877421

Free energy / a.u. = -960.377091

C	-0.71819	0.07658	1.23553
C	0.61156	-0.08730	0.52296
C	1.05721	0.87377	-0.31958
C	0.17901	2.01653	-0.71398
C	-1.25419	1.48707	-0.97674
C	-1.83802	0.77479	0.33234
O	2.29270	0.84018	-0.93199
C	-1.26741	0.62977	-2.26072
C	-2.64402	1.84334	1.11284
C	1.40187	-1.29046	0.74705
O	2.63891	-1.34074	0.05690
C	3.28860	-0.09693	-0.34833
C	4.24231	-0.44968	-1.46956
C	3.93784	0.57388	0.85790
O	1.06680	-2.27436	1.40847
C	-2.85360	-0.27548	-0.13822
O	-4.04772	-0.05098	-0.37553
O	-2.30106	-1.51795	-0.32732
C	-3.19090	-2.58053	-0.82008
C	-0.45744	0.76861	2.60095
H	-1.06562	-0.93325	1.46291
H	0.16823	2.77780	0.07915
H	0.58258	2.49433	-1.61227
H	-1.90138	2.35350	-1.16051
H	-0.84231	1.20536	-3.09122
H	-0.68507	-0.28854	-2.14489
H	-3.46247	2.20846	0.48871
H	3.69021	-0.92479	-2.28300
H	4.72922	0.45437	-1.84495
H	5.00190	-1.14454	-1.10271
H	4.45865	1.48253	0.54380
H	3.18922	0.83907	1.60982
H	4.65649	-0.11357	1.31184
H	-3.54069	-2.33956	-1.82652
H	-2.57450	-3.47679	-0.82076
H	-0.07140	1.78772	2.48386
H	-2.00637	2.68805	1.39082
H	-1.35617	0.81083	3.22263
H	0.29201	0.18579	3.14744
H	-3.08828	1.43443	2.02445
H	-2.28900	0.35481	-2.54185
H	-4.04995	-2.68903	-0.15532

208a



Gas phase:

Potential energy / a.u. = -928.338716987

Free energy / a.u. = -928.063949

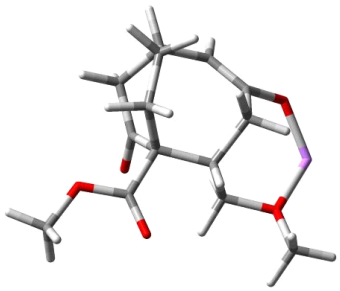
C	-1.84068	-0.67860	1.69206
C	-0.50599	-0.76077	1.46788
C	0.01515	-0.69701	0.00683
C	0.30911	0.82704	-0.35138
C	-0.89097	1.77437	-0.06321
C	-2.18493	1.41225	-0.77324
C	-3.27072	0.70758	0.01772
C	-2.87400	-0.70100	0.58989
C	-2.39716	-1.65954	-0.51925
O	-2.35078	1.69804	-1.97597
O	0.42923	-0.74701	2.43951
C	1.53712	1.36678	0.39765
C	1.31117	-1.48231	-0.18729
O	1.90433	-2.23307	0.63050
O	1.81159	-1.34234	-1.44055
C	3.03928	-2.07637	-1.79790
O	1.82393	2.69006	-0.13123
C	2.88300	3.37845	0.57239
H	-2.17655	-0.59063	2.72165
H	0.52975	0.86844	-1.42416
H	-0.57982	2.76324	-0.41338
H	-1.05583	1.81767	1.01649
H	-3.55273	1.34632	0.86718
H	-4.14135	0.60609	-0.64023
H	-3.80835	-1.10631	1.00355
H	-2.38253	-2.67097	-0.09529
H	-3.10402	-1.66933	-1.36021
H	2.41663	0.72113	0.23674
H	1.34176	1.40943	1.47704
H	3.22094	-1.80768	-2.83575
H	3.86415	-1.75854	-1.15757
H	2.87724	-3.14985	-1.68738
H	3.83699	2.83456	0.49796
H	2.98617	4.35336	0.09365
H	2.63700	3.51586	1.63528
C	-0.99752	-1.30787	-1.06238
H	-1.07629	-0.60036	-1.89131
H	-0.56349	-2.21544	-1.49638
Li	1.66228	-1.93678	2.44516

208b

Gas phase:

Potential energy / a.u. = -928.335511997

Free energy / a.u. = -928.060032



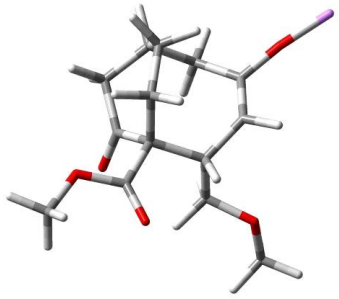
C	-0.77295	-2.31236	1.08555
C	-0.82927	-0.80487	1.07061
C	-0.81656	-0.09362	-0.31512
C	0.53330	0.67475	-0.60772
C	1.64803	-0.23804	-1.17270
C	2.24980	-1.17780	-0.12516
C	1.61857	-2.29853	0.31748
C	0.22246	-2.81418	-0.00030
C	-0.38394	-2.47533	-1.39081
C	-1.15890	-1.12265	-1.44705
O	3.41400	-0.72524	0.39012
O	-0.90345	-0.12342	2.10768
C	1.02418	1.46205	0.62614
C	-1.94465	0.94922	-0.26537
O	-1.83628	2.16062	-0.48727
O	-3.14714	0.36770	0.04586
C	-4.30708	1.26137	0.18998
O	2.31187	2.16884	0.36631
C	2.19383	3.42135	-0.37065
H	-0.47393	-2.62977	2.08830
H	-1.78819	-2.70240	0.89796
H	0.26421	1.40324	-1.38496
H	1.27190	-0.76452	-2.05110
H	2.46020	0.39975	-1.54073
H	2.13022	-2.84856	1.10564
H	0.25503	-3.91032	0.07362
H	-1.10033	-3.26734	-1.64577
H	0.40091	-2.52191	-2.15045
H	-2.22992	-1.33096	-1.36634
H	-1.00997	-0.63451	-2.41835
H	0.29298	2.20604	0.95003
H	1.25049	0.79822	1.45910
H	-5.13594	0.60068	0.43485
H	-4.48898	1.79615	-0.74440
H	-4.12410	1.97813	0.99285
H	3.18924	3.86875	-0.39213
H	1.49797	4.09292	0.14249
H	1.84462	3.24454	-1.39287
Li	3.70686	0.94855	0.66380

208c

Gas phase:

Potential energy / a.u. = -928.298983146

Free energy / a.u. = -928.027105



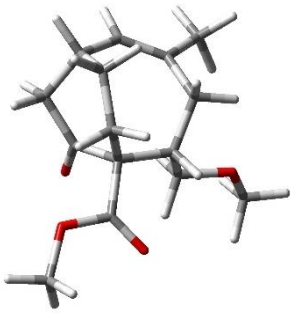
C	-0.12829	-2.06232	1.58211
C	-0.75478	-0.73757	1.21172
C	-0.73202	-0.33353	-0.27887
C	0.27980	0.85157	-0.58998
C	1.70769	0.47330	-0.93529
C	2.55806	-0.35171	-0.28007
C	2.17986	-1.15818	0.95570
C	1.13424	-2.31352	0.72968
C	0.71204	-2.50361	-0.74775
C	-0.45612	-1.57613	-1.19353
O	3.82454	-0.55834	-0.71528
O	-1.25346	0.01354	2.06745
C	0.83737	4.31000	0.69035
C	-2.15142	0.15917	-0.61202
O	-2.46201	1.20633	-1.18397
O	-3.09509	-0.76812	-0.22543
C	-4.50317	-0.41576	-0.45647
O	0.82193	3.15052	-0.16937
C	0.20869	1.98576	0.45443
H	0.08923	-2.04786	2.65496
H	-0.87118	-2.85604	1.40598
H	2.11072	0.98920	-1.80266
H	3.10812	-1.58504	1.34763
H	1.80148	-0.48093	1.73392
H	1.58086	-2.35919	-1.39528
H	0.38400	-3.54413	-0.87675
H	-1.37891	-2.16476	-1.22443
H	-0.27397	-1.20867	-2.20917
H	1.42327	4.12954	1.60473
H	1.30305	5.11387	0.11678
H	-5.06797	-1.26572	-0.07860
H	-4.75302	0.49644	0.08913
H	-4.68445	-0.26264	-1.52254
H	-0.82861	2.21488	0.72858
H	0.75668	1.72660	1.37137
H	1.59240	-3.25016	1.07131
H	-0.17971	4.61318	0.98137
H	-0.14274	1.30248	-1.49572
Li	5.33060	-0.62579	-1.28927

217

Gas phase:

Potential energy / a.u. = -885.444957325

Free energy / a.u. = -885.136356



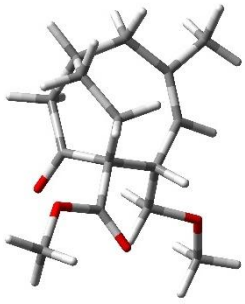
C	-0.57733	-2.16092	1.32293
C	-0.72961	-0.67054	1.12819
C	-0.81115	-0.14457	-0.32637
C	0.47649	0.65050	-0.76049
C	1.66630	-0.22461	-1.23684
C	2.33331	-1.09812	-0.18001
C	1.76932	-2.16556	0.41861
C	0.37688	-2.75368	0.25108
C	-0.27531	-2.59959	-1.14970
O	-0.78764	0.11749	2.08574
C	0.93246	1.68037	0.28594
C	-2.00883	0.82001	-0.37733
O	-2.02092	1.96088	-0.84579
O	-3.13671	0.22637	0.13877
C	-4.35800	1.04529	0.18826
O	1.99184	2.46705	-0.33801
C	2.41823	3.59048	0.46836
H	-0.21649	-2.33744	2.34045
H	0.15629	1.23812	-1.63074
H	1.34659	-0.82390	-2.09493
H	2.36382	-2.67848	1.17611
H	0.46658	-3.82937	0.45332
H	-0.93585	-3.46124	-1.31071
H	0.49902	-2.66465	-1.91888
H	0.10170	2.33572	0.57068
H	1.31883	1.20138	1.19404
H	-5.11060	0.39393	0.62761
H	-4.64308	1.35817	-0.81831
H	-4.18822	1.92633	0.81017
H	2.82265	3.26262	1.43729
H	1.58918	4.28889	0.65085
H	3.20137	4.09642	-0.09872
C	-1.13630	-1.31516	-1.31588
H	-1.05719	-0.93233	-2.34058
H	-2.18729	-1.57818	-1.16190
H	-1.57212	-2.62680	1.23660
C	3.74430	-0.67858	0.18124
H	3.76781	0.37631	0.48271
H	4.16094	-1.28711	0.99021
H	4.41054	-0.76609	-0.68921
H	2.40853	0.48151	-1.61960

218

Gas phase:

Potential energy / a.u. = -885.435942701

Free energy / a.u. = -885.129300



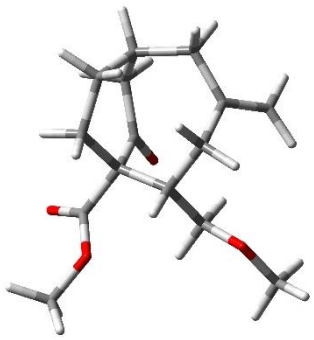
C	0.53839	-1.60388	1.71099
C	-0.53874	-0.64786	1.24498
C	-0.64623	-0.30843	-0.25197
C	0.34213	0.87189	-0.54495
C	1.83116	0.58137	-0.63335
C	2.66954	-0.45603	-0.42413
C	2.46573	-1.90843	0.00811
C	1.15107	-2.47655	0.59440
C	0.07906	-2.78255	-0.46814
O	-1.27654	-0.07655	2.06678
C	0.13619	2.07863	0.40341
C	-2.08512	0.14092	-0.52578
O	-2.44981	1.21384	-1.01453
O	-2.96774	-0.86411	-0.21486
C	-4.39801	-0.56718	-0.38106
O	0.79486	3.21276	-0.22716
C	0.66167	4.44342	0.52164
H	1.31292	-1.01102	2.21859
H	0.04085	1.24964	-1.53371
H	2.32404	1.50470	-0.93347
H	3.24793	-2.09745	0.76108
H	2.75024	-2.54485	-0.84747
H	1.43761	-3.43393	1.05189
H	-0.79680	-3.22899	0.02404
H	0.45760	-3.52485	-1.18236
H	-0.92885	2.29210	0.53626
H	0.58468	1.89002	1.38947
H	-4.90645	-1.48764	-0.10153
H	-4.61068	-0.29536	-1.41709
H	-4.68355	0.25488	0.27833
H	1.12344	4.36191	1.51673
H	-0.39364	4.72583	0.64314
H	1.17870	5.21111	-0.05618
C	-0.34331	-1.51572	-1.21878
H	0.44925	-1.21267	-1.90931
H	-1.22901	-1.73266	-1.82271
H	0.07856	-2.22771	2.48765
C	4.15583	-0.20474	-0.66815
H	4.73905	-0.35011	0.25235
H	4.55919	-0.90918	-1.40972
H	4.34251	0.80949	-1.03105

219

Gas phase:

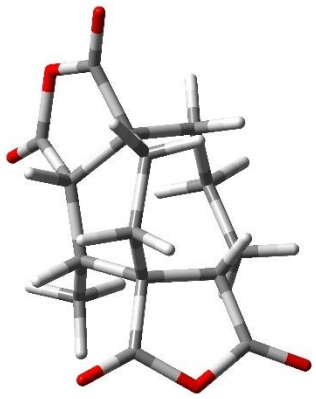
Potential energy / a.u. = -885.438115285

Free energy / a.u. = -885.129259



C	1.89833	-1.49914	1.21972
C	0.54258	-0.83018	1.21200
C	-0.25424	-0.83451	-0.11443
C	-0.34844	0.61317	-0.71735
C	0.99167	1.19145	-1.26765
C	3.18261	0.16333	-0.27051
C	2.69401	-1.30157	-0.08936
C	1.89552	-1.85188	-1.30681
O	0.06556	-0.30491	2.22949
C	-1.00788	1.60885	0.25138
C	-1.64418	-1.41178	0.20183
O	-1.85309	-2.31983	1.01228
O	-2.63681	-0.91080	-0.60505
C	-3.97901	-1.49295	-0.43626
O	-1.22922	2.83981	-0.50095
C	-1.89310	3.86858	0.26974
H	2.45105	-1.13469	2.09139
H	-1.02630	0.53084	-1.57471
H	1.29211	0.61997	-2.15185
H	3.61082	-1.90034	-0.00239
H	2.21005	-2.88639	-1.49490
H	2.17261	-1.28927	-2.20425
H	-1.96895	1.22229	0.61196
H	-0.37425	1.81282	1.12128
H	-4.60231	-0.96003	-1.15113
H	-4.32697	-1.33854	0.58688
H	-3.95297	-2.56313	-0.65168
H	-1.99420	4.73139	-0.39077
H	-1.30648	4.15238	1.15555
H	-2.89038	3.54244	0.59915
C	0.35479	-1.87109	-1.12357
H	-0.14521	-1.74144	-2.09068
H	0.07008	-2.86476	-0.75706
H	1.72293	-2.57610	1.37627
C	2.28799	2.34492	0.52274
H	1.60083	3.18446	0.47658
H	3.09892	2.41978	1.24223
H	0.74250	2.19884	-1.61380
H	3.73550	0.19919	-1.22379
H	3.91545	0.37698	0.51850
C	2.14495	1.27433	-0.27795

cis-237



Gas phase:

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Free energy / a.u. = -1031.989466

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C	-1.15144	0.30297	0.57091
C	-1.60258	-0.93537	-0.27403
C	-1.08071	-1.19326	-1.71024
C	0.45331	-1.20468	-1.88757
C	1.29029	-1.67391	-0.68476
C	1.51622	-0.66848	0.52976
C	0.71885	-1.04380	1.79960
C	-0.57432	-0.18659	1.94663
C	-2.46442	1.03445	0.87508
O	-3.56467	0.30142	0.38432
C	-3.12466	-0.85692	-0.30664
O	-2.61689	2.08739	1.47030
O	-3.91610	-1.61678	-0.83249
H	-1.36989	-1.83942	0.30360
C	-0.48691	1.98443	-1.38302
C	3.03348	-0.65527	0.70315
O	3.54752	0.33420	-0.19772
C	2.48407	1.18815	-0.64450
O	3.76811	-1.33066	1.39702
O	2.65925	2.00972	-1.52352
H	1.60087	1.32599	1.19517
H	-0.27054	2.20373	0.68748
H	-1.48731	-2.17096	-1.99462
H	-1.52517	-0.47567	-2.40770
H	0.81241	-0.22199	-2.20663
H	0.68202	-1.87590	-2.72532
H	2.27427	-1.94768	-1.08442
H	0.88013	-2.60178	-0.26951
H	0.47309	-2.11007	1.78055
H	1.34299	-0.89552	2.68884
H	-0.38051	0.70096	2.56007
H	-1.33661	-0.76754	2.47955
H	-1.49656	2.40971	-1.34830
H	0.20906	2.80001	-1.59520
H	-0.43798	1.29598	-2.22455

trans-237

Gas phase:

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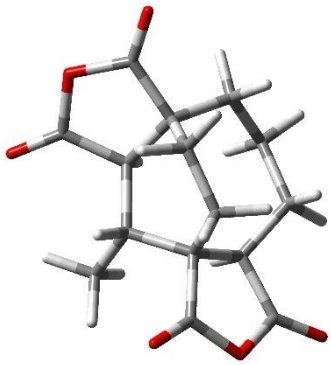
Free energy / a.u. = -1032.020616



C	1.22853	0.46395	-0.65202
C	-0.01857	1.29878	-0.23102
C	-1.10909	0.36746	0.39453
C	-1.75629	-0.64554	-0.60593
C	-1.31161	-2.12218	-0.63771
C	0.09972	-2.37297	-1.19656
C	1.29821	-2.15466	-0.24985
C	1.59627	-0.71706	0.29544
C	0.98596	-0.45765	1.70372
C	-0.54903	-0.29968	1.70185
C	-2.30160	1.23228	0.82698
O	-3.51365	0.62634	0.42596
C	-3.25368	-0.54159	-0.33433
O	-2.29163	2.27161	1.46206
O	-4.15327	-1.28045	-0.68852
H	-1.62662	-0.24994	-1.62478
C	-0.51864	2.17456	-1.39640
C	3.11358	-0.58696	0.46362
O	3.55793	0.64180	-0.08689
C	2.48588	1.32726	-0.70788
O	3.88880	-1.35940	0.99605
O	2.64489	2.43542	-1.18794
H	1.06655	0.09198	-1.67258
H	0.27761	1.98042	0.57726
H	-2.03779	-2.64040	-1.27527
H	-1.41071	-2.57974	0.35418
H	0.15068	-3.42524	-1.50607
H	0.23249	-1.79428	-2.12195
H	1.19795	-2.82254	0.61497
H	2.18993	-2.50472	-0.78455
H	1.28401	-1.26992	2.37490
H	1.43488	0.45850	2.10908
H	-1.03783	-1.26476	1.86010
H	-0.81902	0.32853	2.55754
H	-1.35413	2.80839	-1.08390
H	0.28897	2.82915	-1.73324
H	-0.83933	1.57606	-2.25815

4.6. X-Ray Crystallography

X-ray diffraction experiments on **24**, **38a**, **39e**, and **57** were carried out at 100(2) K on a Bruker APEX II diffractometer using Mo-K_α radiation (λ = 0.71073 Å). Intensities were integrated in SAINT[219] and absorption corrections based on equivalent reflections were applied using SADABS.[220] Structure **57** was solved using ShelXS,[221] **39e** was solved using Superflip[222,223] and both **24** and **38a** were solved using ShelXT[224] all of the structures were refined by full matrix least squares against F^2 in ShelXL[221,224] using Olex2.[225] All non-hydrogen atoms were refined anisotropically. While all hydrogen atoms were located geometrically and refined using a riding model, apart from the N-H protons in **57** and **38a** which were located in the difference map and refined freely. In the case of **57**, the structure was refined as a two-component twin giving a refined twin scale fraction of 0.4712(12). In **38a** one of the methanol solvent molecules was found to have disorder in the position of the oxygen, the occupancies were refined with the sum of the two sites set to equal 1. Restraints and constraints were applied to maintain sensible thermal and geometric parameters. Crystal structure and refinement data are given in Table 1. Crystallographic data for compounds **24**, **38a**, **39e**, and **57** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 1897232-1897235. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax(+44) 1223 336033, e-mail: deposit@ccdc.cam.ac.uk].

Table 13 – Crystal data and structure refinement for **24**, **38a**, **39e**, and **57**

	24	**38a**	**39e**	**57**
Empirical formula	$C_{22}H_{21}NO_4$	$C_{32.5}H_{37}N_3O_{6.5}S$	$C_{22}H_{19}ClFNO_3$	$C_{29}H_{26}N_2O_4$
Formula weight	363.40	605.71	399.83	466.52
Temperature/K	100(2)	100(2)	100(2)	100(2)
Crystal system	monoclinic	triclinic	orthorhombic	monoclinic
Space group	$P2_1/n$	P-1	$P2_12_12_1$	$P2_1/c$
a/Å	12.1811(2)	11.5641(3)	6.7377(3)	12.8112(7)
b/Å	5.97140(10)	14.4286(4)	9.7118(4)	11.0276(6)
c/Å	24.6196(4)	18.7388(5)	29.7329(13)	16.7741(12)
α/°	90	81.9854(14)	90	90
β/°	91.9220(10)	89.0809(14)	90	91.898(4)
γ/°	90	83.9594(14)	90	90
Volume/Å^3	1789.78(5)	3078.91(14)	1945.58(15)	2368.5(2)
Z	4	4	4	4
ρ_{calc}g/cm^3	1.349	1.307	1.365	1.308
μ/mm^{-1}	0.093	0.156	0.229	0.088
F(000)	768.0	1284.0	832.0	984.0
Crystal size/mm^3	0.512 × 0.338 × 0.283	0.438 × 0.328 × 0.305	0.375 × 0.361 × 0.072	0.359 × 0.198 × 0.13
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2θ range for data collection/°	3.682 to 55.896	3.36 to 55.94	2.74 to 54.374	3.18 to 52.884
Index ranges	-16 ≤ h ≤ 16, -6 ≤ k ≤ 7, -32 ≤ l ≤ 32	-11 ≤ h ≤ 15, -19 ≤ k ≤ 19, -23 ≤ l ≤ 24	-8 ≤ h ≤ 8, -12 ≤ k ≤ 11, -38 ≤ l ≤ 38	-16 ≤ h ≤ 16, 0 ≤ k ≤ 13, 0 ≤ l ≤ 21
Reflections collected	15153	57146	32309	4984
Data/restraints/ parameters	4282/0/244	14790/1/798	4315/0/253	4984/0/321
Goodness-of-fit on F^2	1.022	1.030	1.097	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0376, wR_2 = 0.0882	R_1 = 0.0466, wR_2 = 0.1068	R_1 = 0.0449, wR_2 = 0.1026	R_1 = 0.0534, wR_2 = 0.0955
Final R indexes [all data]	R_1 = 0.0476, wR_2 = 0.0937	R_1 = 0.0715, wR_2 = 0.1193	R_1 = 0.0505, wR_2 = 0.1054	R_1 = 0.0901, wR_2 = 0.1086
Largest diff. peak/hole / e Å^{-3}	0.30/-0.21	0.42/-0.48	0.39/-0.29	0.32/-0.27

Chapter 5: References

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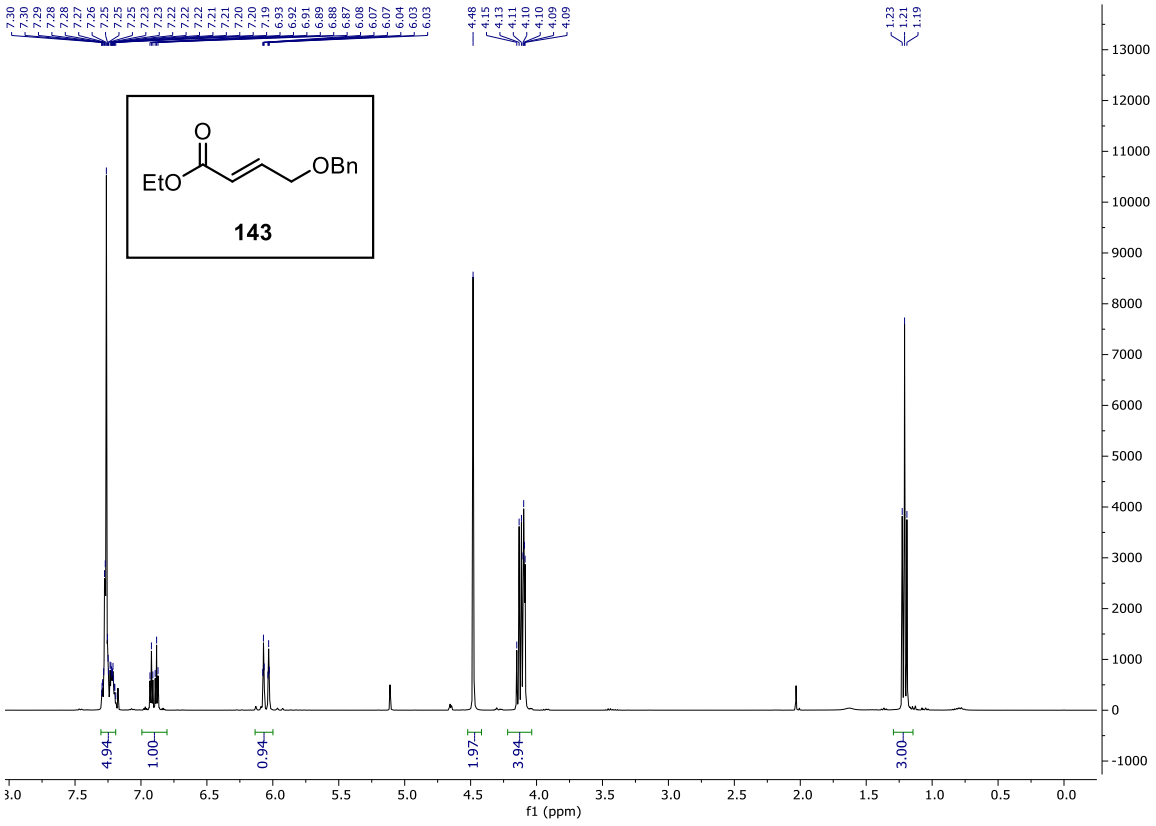
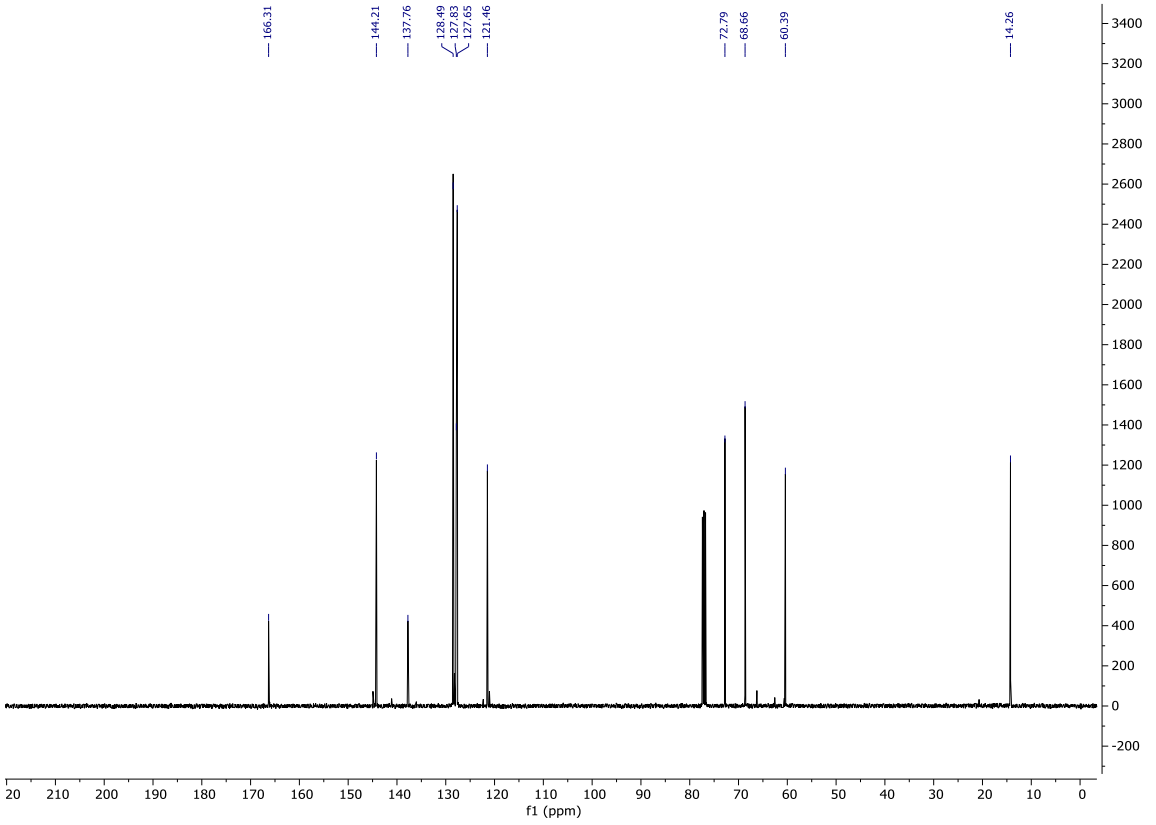
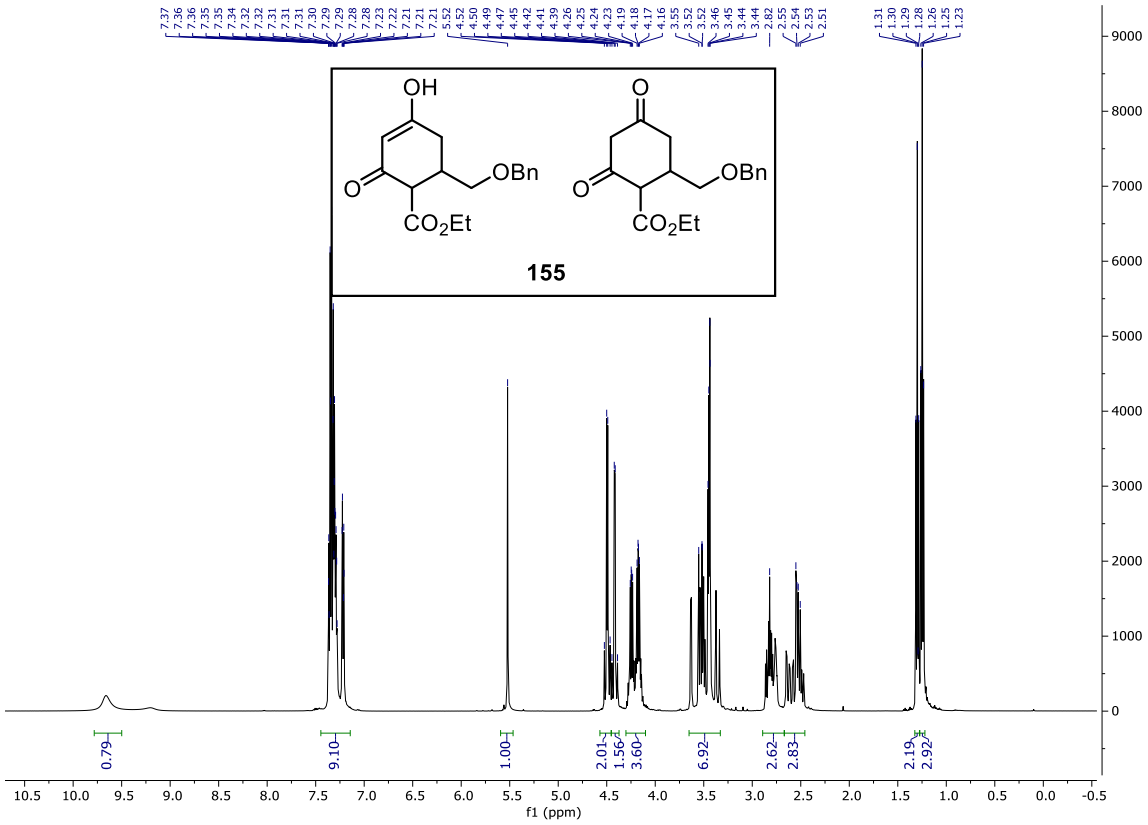
Chapter 6: Appendix

6. Appendix

6.1. Selected Spectra



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CO2Et
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OBn
CO2Et
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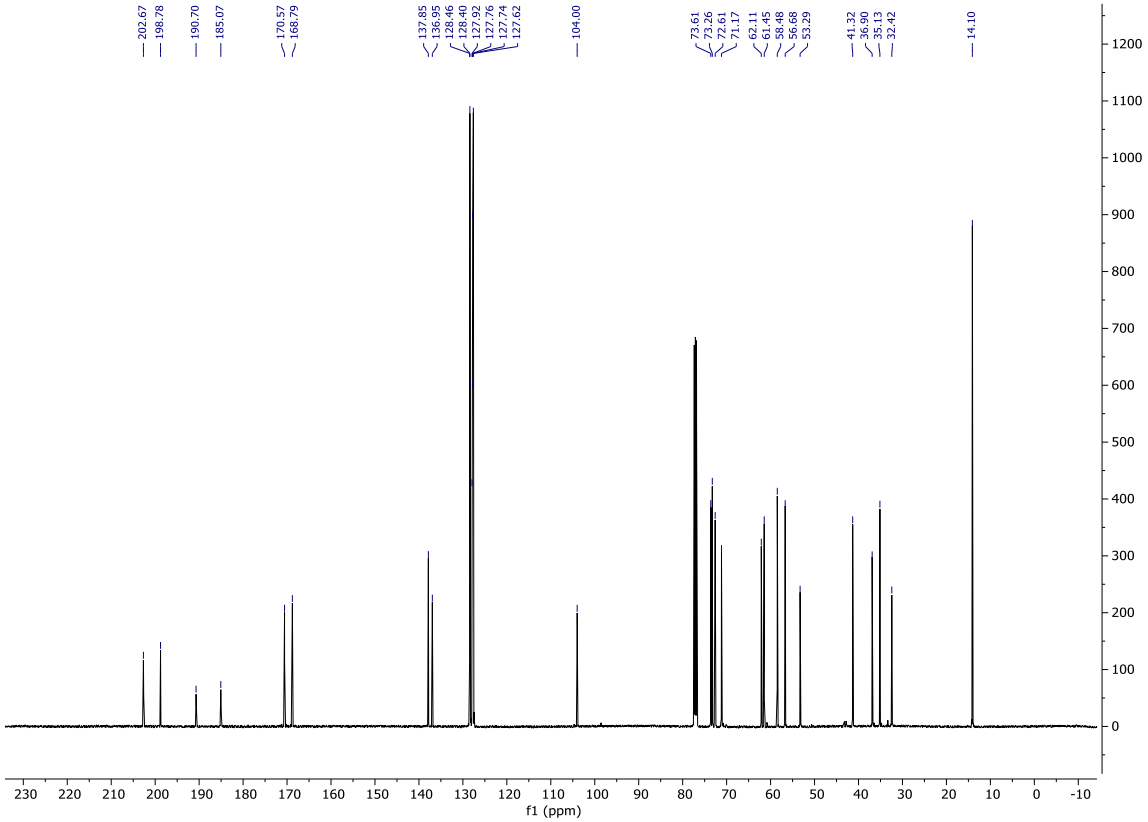
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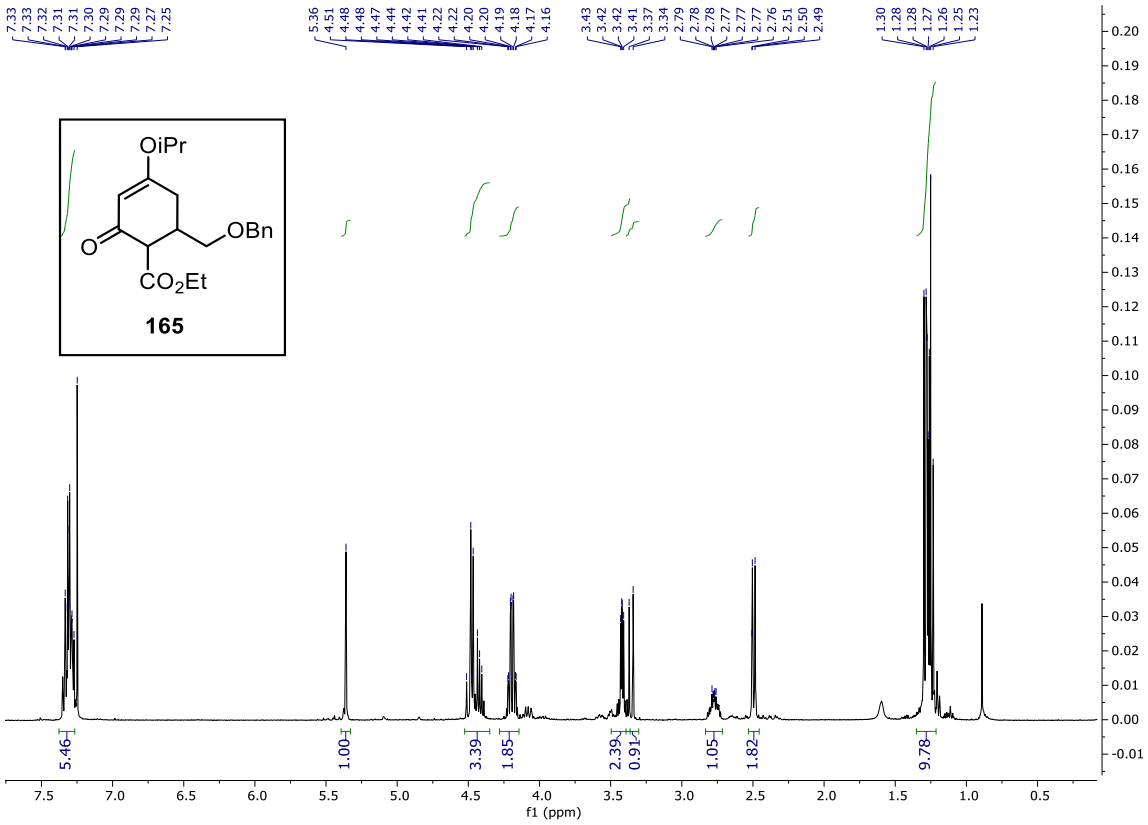
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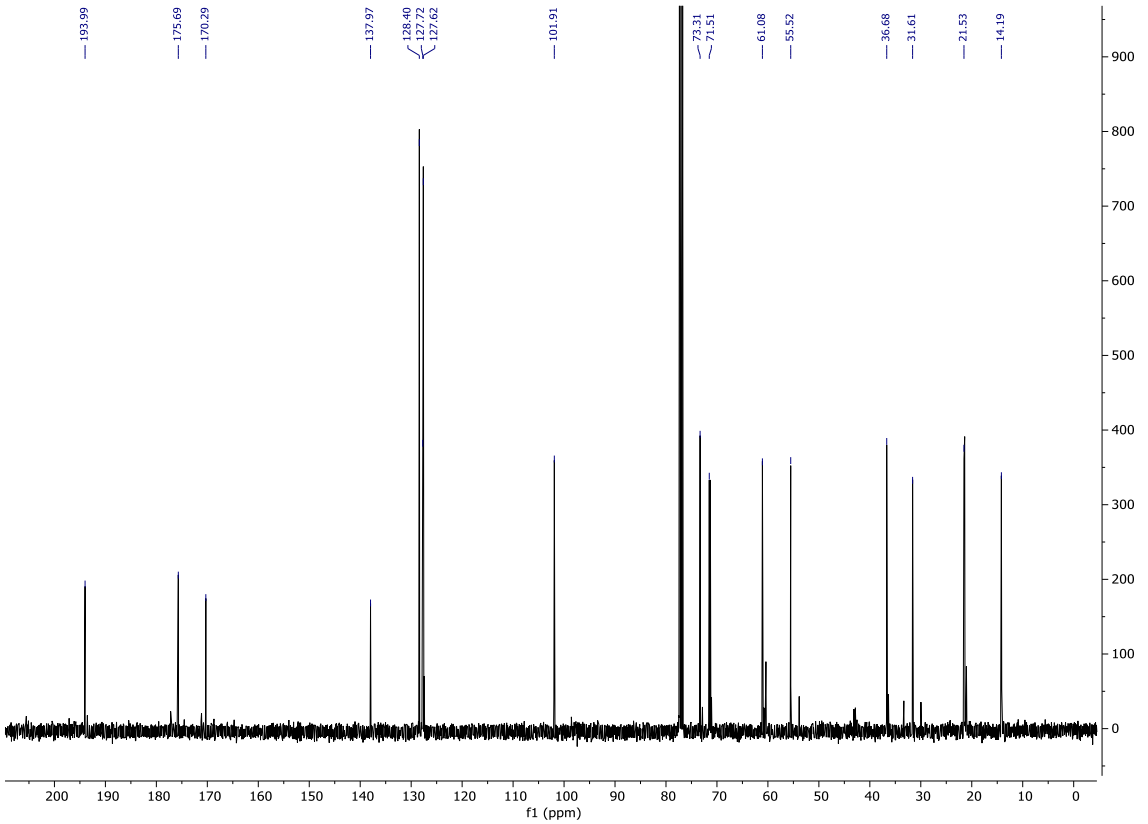
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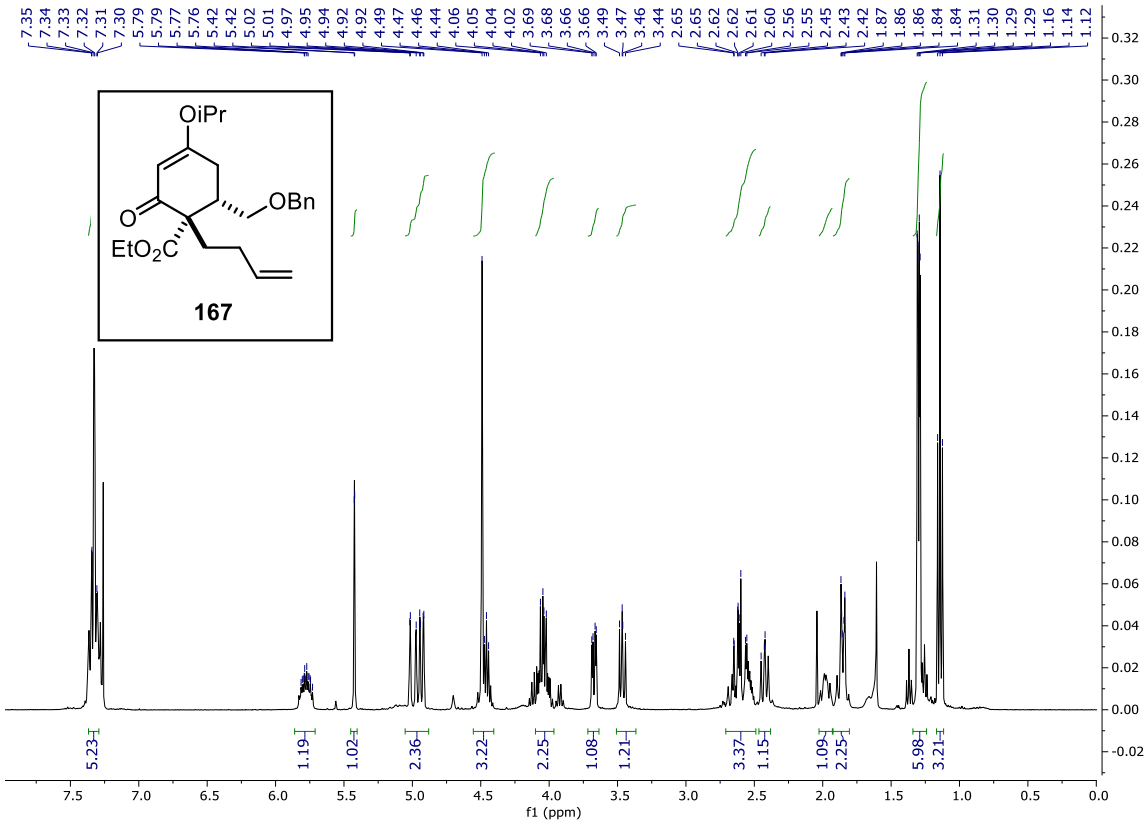
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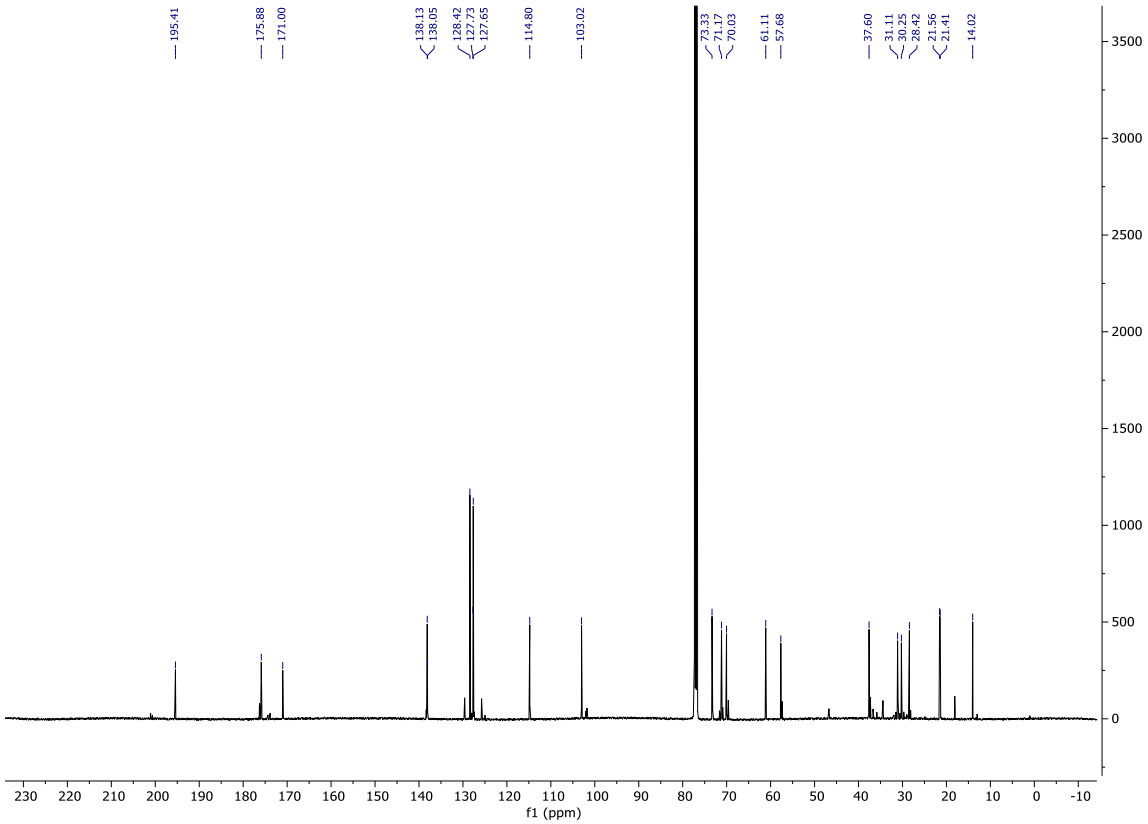
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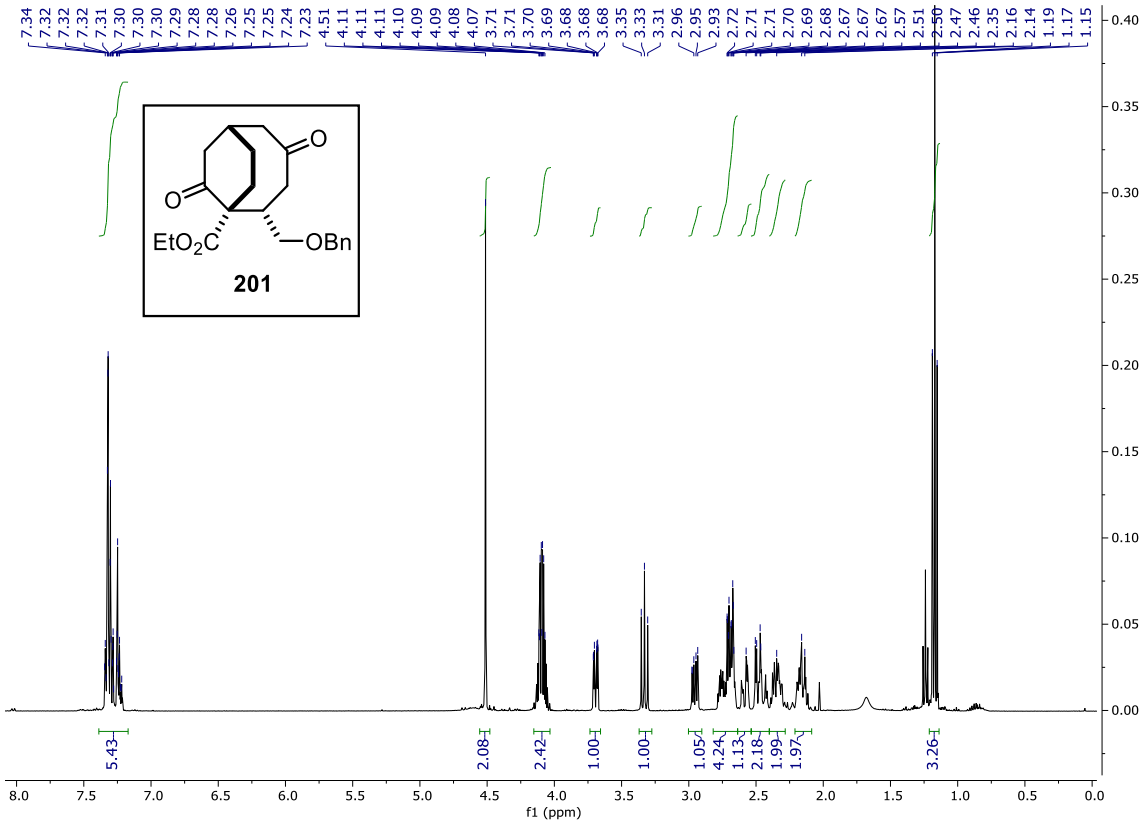
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O
O
EtO2C
OBn
201
5.43
2.08
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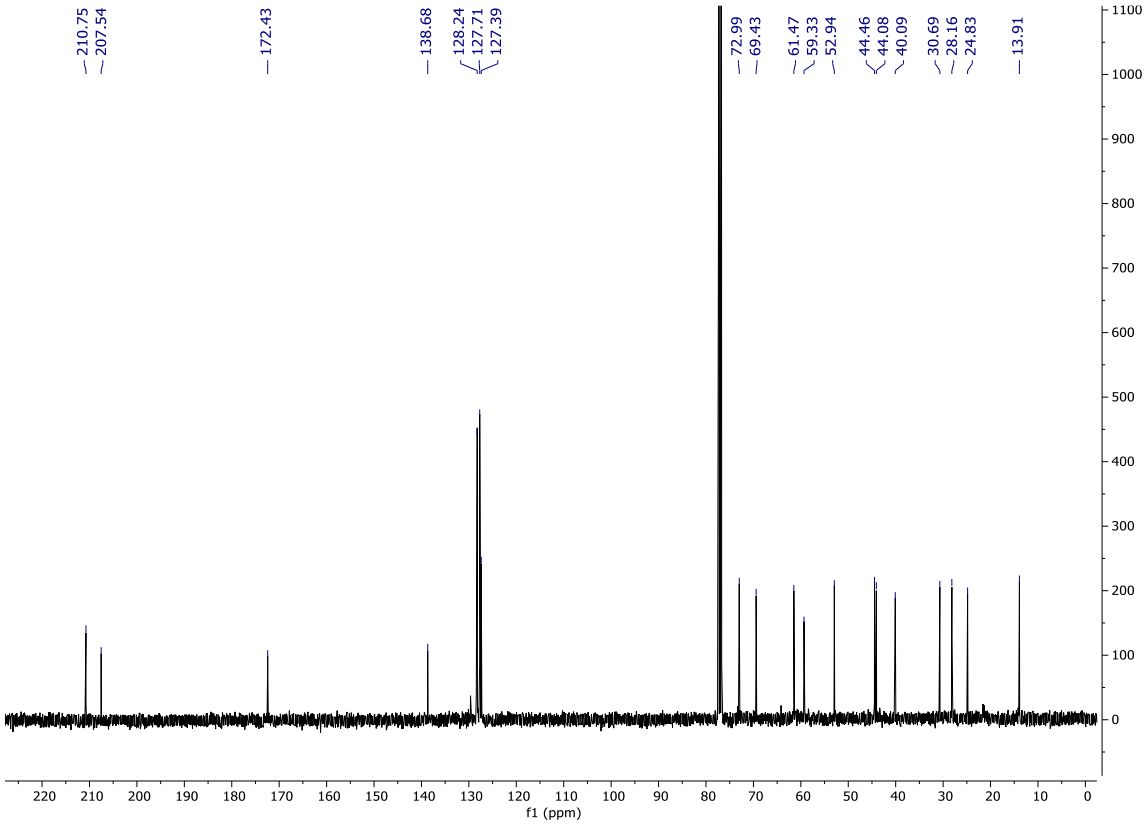
1.00
1.00
1.05
4.24
1.13
2.18
1.99
1.97
3.26
f1 (ppm)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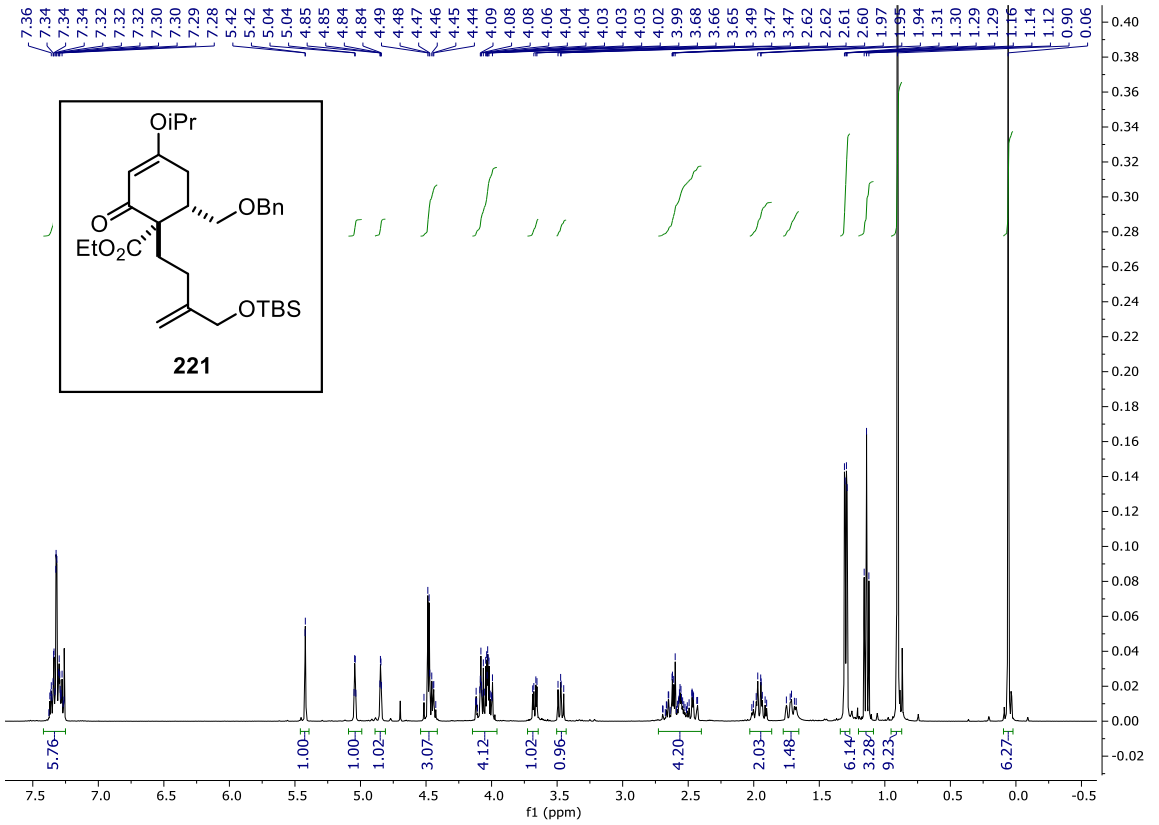
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OTBS
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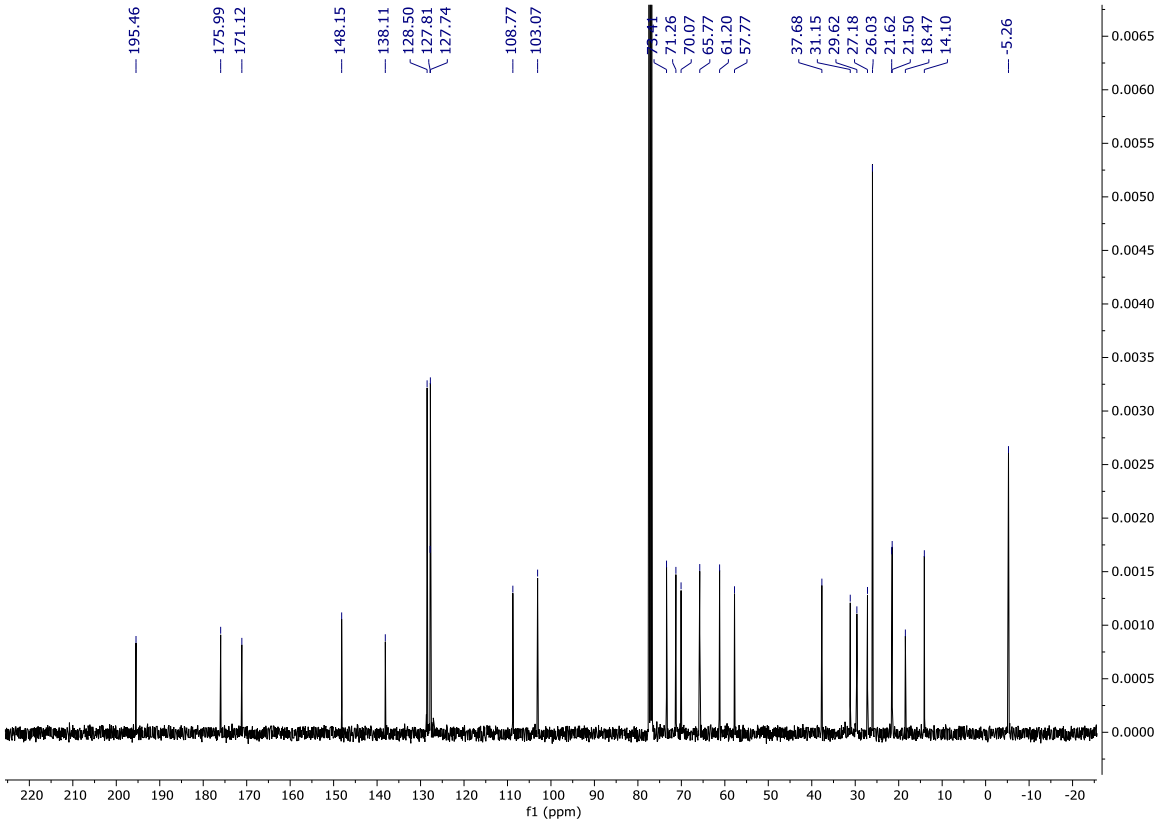
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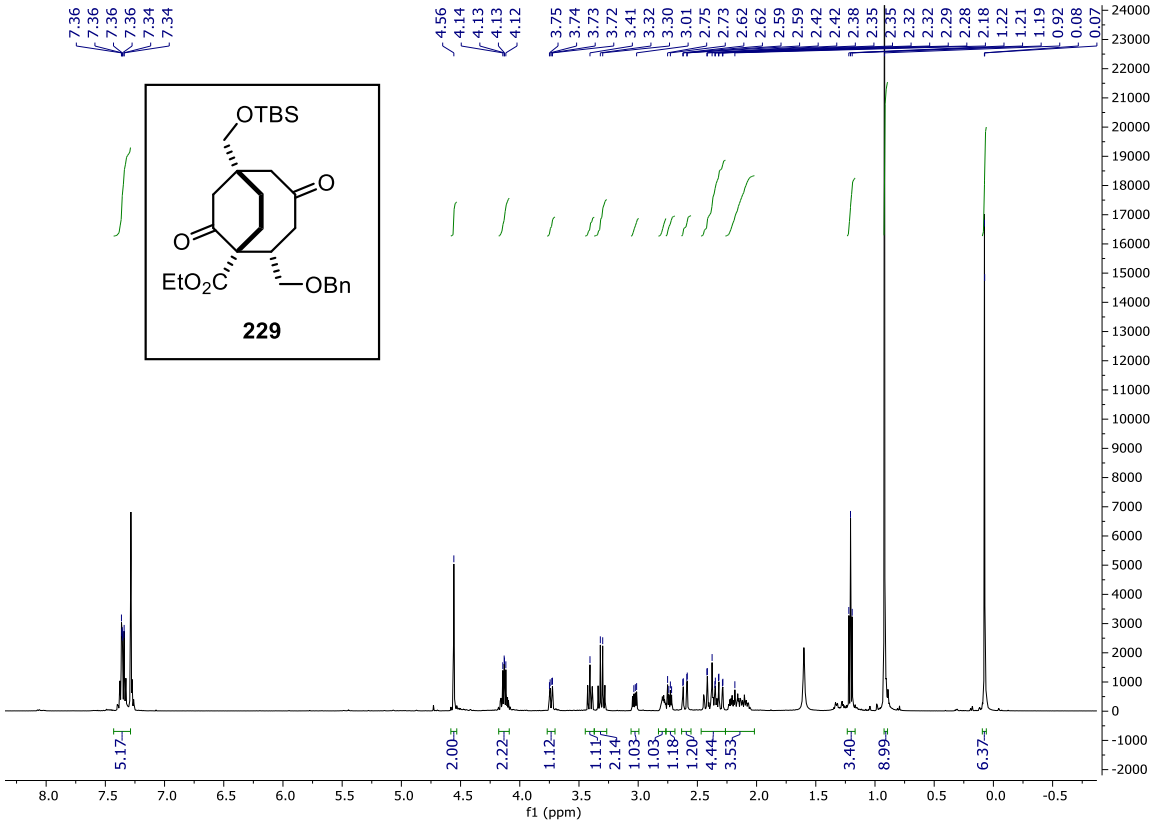
f1 (ppm)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OBn
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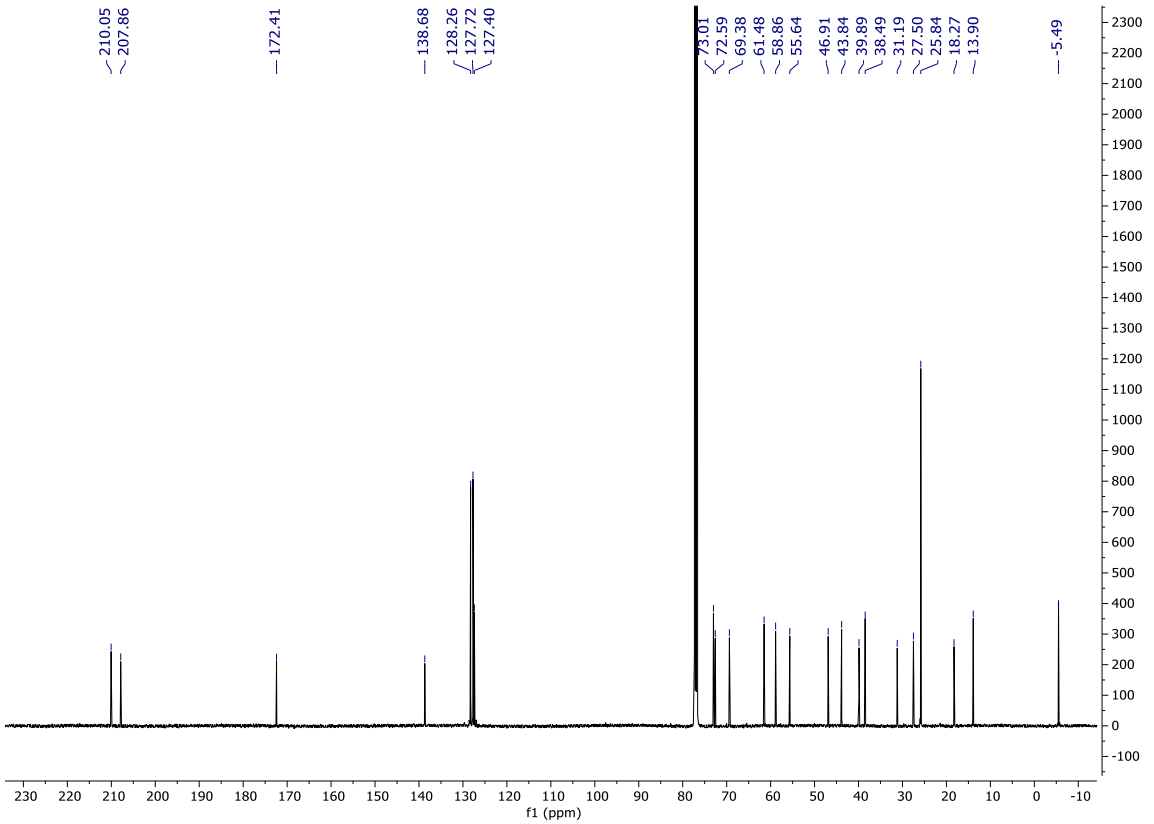
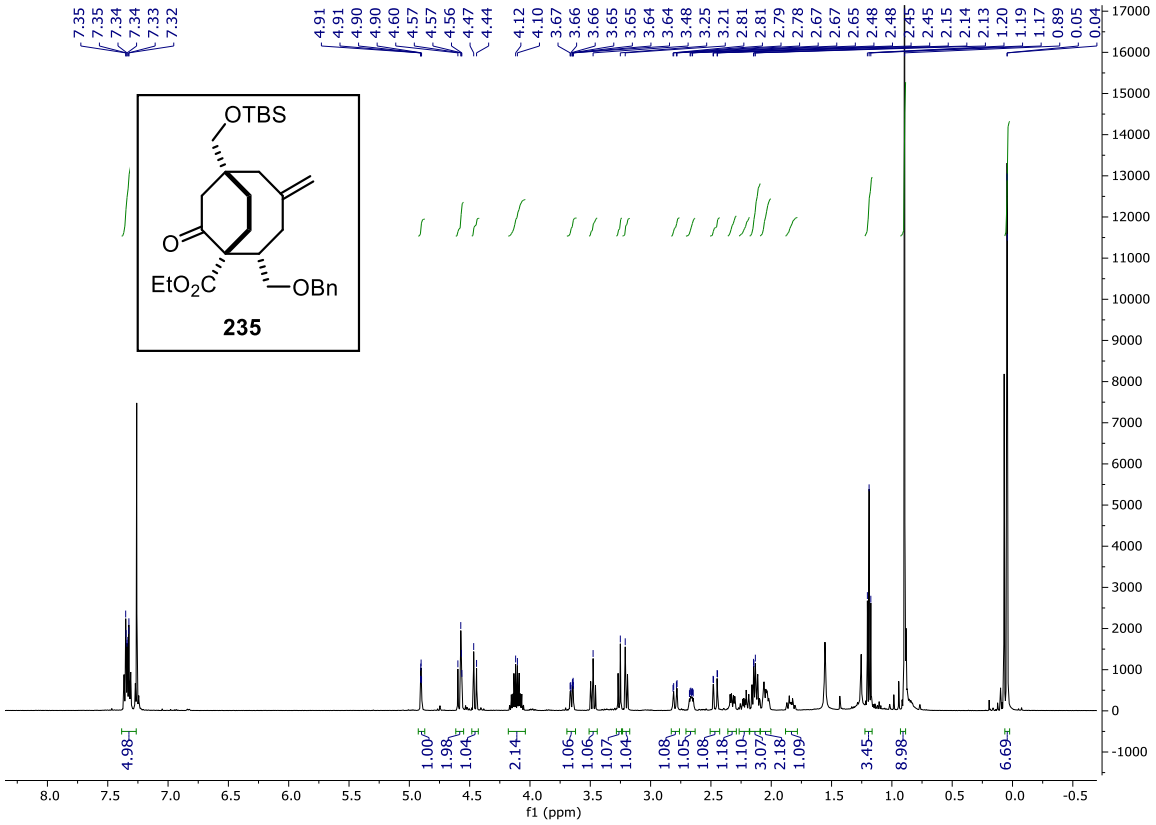
f1 (ppm)


f1 (ppm)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OBn
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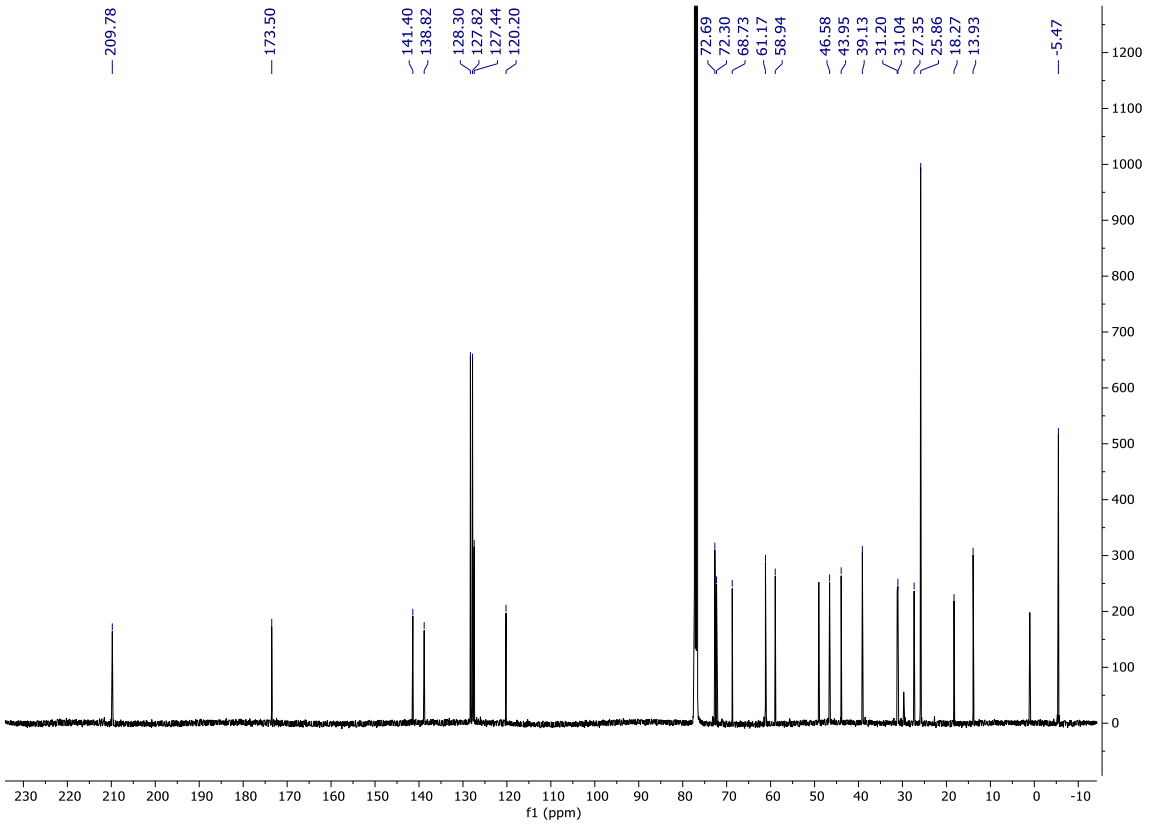
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-5.47
f1 (ppm)

Cyclisation

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Sequential Photochemical and Prins Reactions for the Diastereoselective Synthesis of Tricyclic Scaffolds

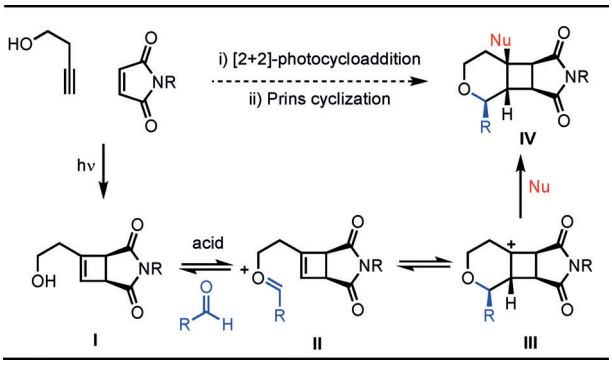
*Bethan L. Donnelly, Luke D. Elliott, Christine L. Willis, and Kevin I. Booker-Milburn**

Abstract: *Cyclobutene alcohols undergo Prins cyclisations to generate single diastereomers of novel tricyclic heterocycles with five contiguous stereocentres. The reaction times are significantly shorter (ca. 15 min) than with traditional alkene substrates. Stereoselective aza-Prins cyclisations of cyclobutene amine derivatives give fused aza-heterocyclic scaffolds. Computational studies provide insight into the observed stereocontrol. The modular approach is flexible, enabling the introduction of a variety of functional groups (including amides, nitriles, alkynes, and arenes) into the sp³-rich heterocyclic scaffolds.*

There is debate within medicinal chemistry that sp³-rich structures are underrepresented in drug discovery, and new methods for the synthesis of easily diversifiable, sp³-rich scaffolds are desirable.[1–3] Multicomponent reactions offer an elegant solution where simple starting materials can be used to quickly generate molecular complexity. Synthesis of novel fused cyclobutane ring systems in this way would access new areas of chemical space, whilst retaining some of the conformational restriction often associated with successful drug molecules. Similar cyclobutane fused ring systems have previously been shown to have potential as bioisosteres for common building blocks in drug discovery.[4]

The Prins cyclisation of an oxocarbenium ion generated in situ, for example, from the acid-mediated reaction of a homoallylic alcohol and an aldehyde, is a powerful method for the synthesis of functionalized tetrahydropyrans.[5,6] It has been used to good effect in the synthesis of natural products, such as bryostatin,[7] (+)-dactylolide,[8] and (−)-blepharocalyxin D;[9] however, to the best of our knowledge, cyclobutene alcohols have not been reported as substrates in Prins cyclizations. This may reflect, in part, limited approaches for the synthesis of 2-cyclobutenylethanol and its derivatives compared to other substituted cyclobutenes.[10]

Recently, our group developed an efficient photochemical synthesis of bicyclic cyclobutene alcohols **I** on multigram scales.[11–13] We envisaged that such compounds would undergo Prins cyclization via intermediates **II** and **III** to generate sp³-rich polyheterocycles **IV** possessing several sites available for further library diversification (Scheme 1).



Scheme 1. Proposed synthesis of tricyclic heterocycles.

Herein, we report the results of studies leading to the selective synthesis of 6,4,5-tricyclic scaffolds with five contiguous stereocentres, decorated with a range of useful further functionality.

Succinimide **1** was synthesized by the [2+2] cycloaddition of maleimide with homopropargyl alcohol. The imide can be subsequently *N*-benzyl- or methylated, or alternatively, the photochemical reaction can be performed directly with *N*-methyl- or *N*-benzyl maleimide. All routes can be carried out on a large scale with the aid of flow photochemistry (Scheme 2a).

Initial investigations were based on tandem Prins–Ritter reaction conditions first reported by Willis and co-workers for the synthesis of 4-amidotetrahydropyrans.[14] Yadav and co-workers have used similar conditions for the formation of 4-amidopiperidine derivatives,[15] and a Sakurai–Prins–Ritter reaction to prepare 2,6-disubstituted tetrahydropyrans has also been developed.[16–18] Thus **1** was treated with benzaldehyde and trifluoromethanesulfonic (triflic) acid in acetonitrile at room temperature. After 30 min, the starting material had been completely consumed. Amide **4a** was isolated as a single diastereomer with creation of three new stereocentres (Scheme 2b). Substituting triflic acid for other protic acids (HCl, H_2SO_4, AcOH) or Lewis acids (BF_3, $InCl_3$) returned only starting material in all cases. The reaction conditions employing triflic acid were optimized for temperature (0 °C), concentration (0.2 M), and equivalents of aldehyde (1.2 equiv) and acid (1.5 equiv) with unusually short reaction times (10–60 min).

Further studies revealed acetate **9** and ketone **10** (Scheme 2b) as side products of the reaction. The formation of **9** can be accounted for by reaction of the alcohol **1** with protonated acetonitrile, followed by hydrolysis upon workup. The structure of **10** was confirmed by X-ray crystallography (Scheme 2c). Compound **4a** was re-subjected to the reaction

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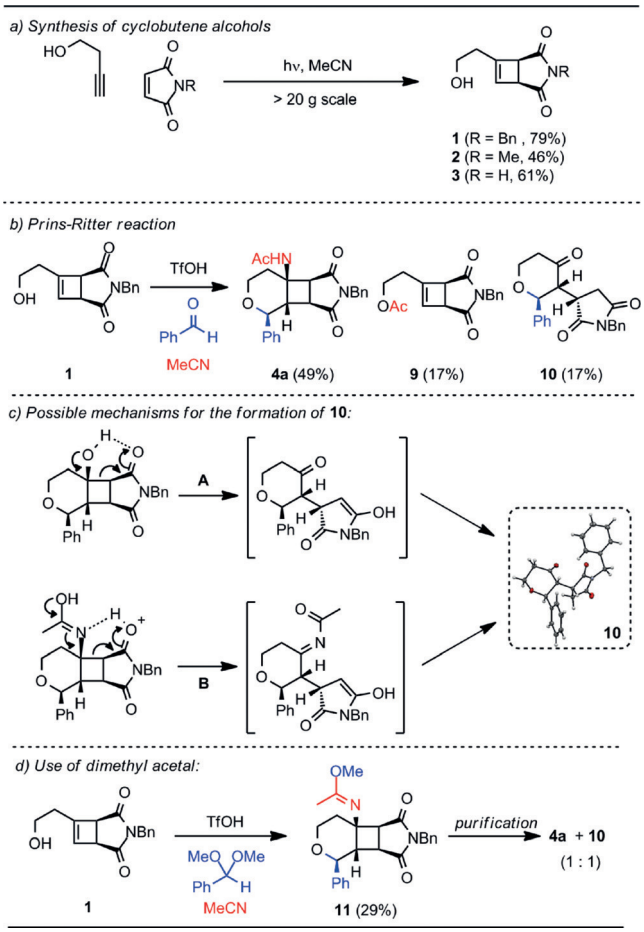
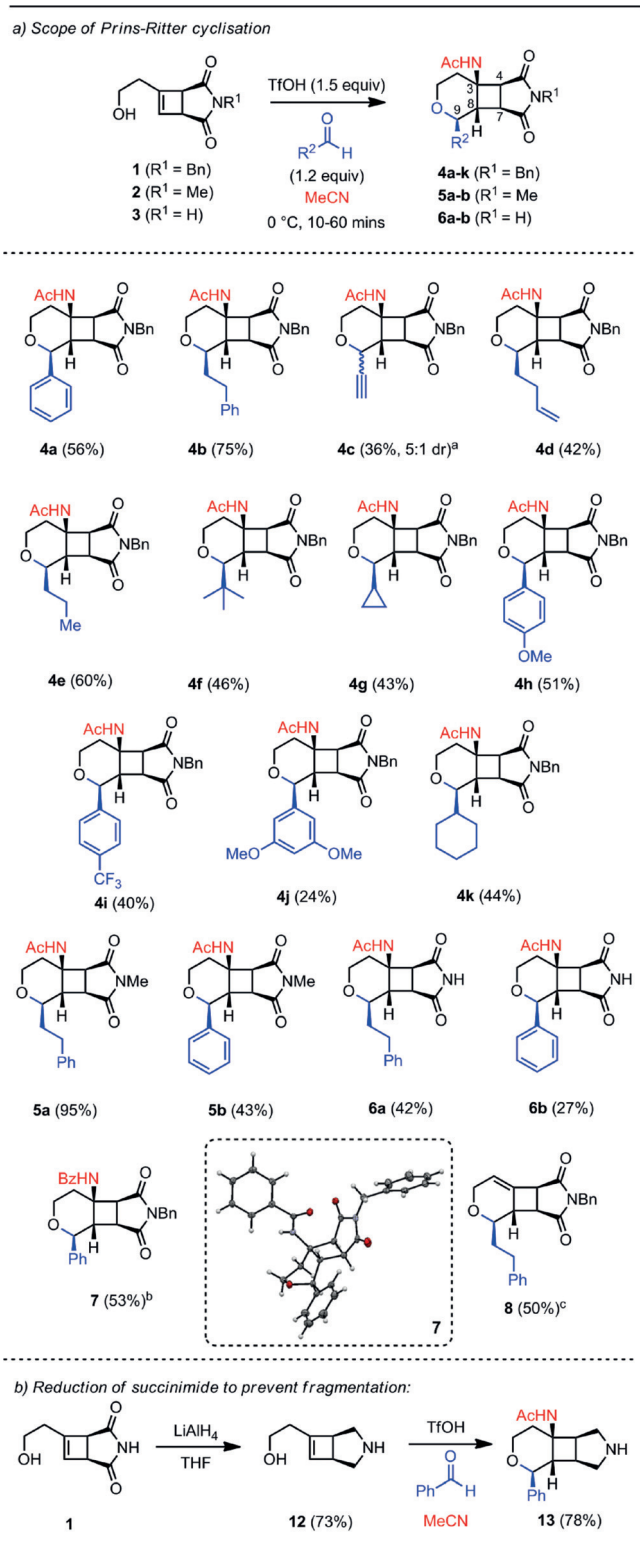
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201903488.



Scheme 2. Application of the Prins cyclisation to cyclobutene alcohols and investigations into side product formation.[22] Bn = benzyl, Tf = trifluoromethanesulfonyl.

conditions and found to be stable, confirming that **10** is formed during the reaction. The mechanism likely involves a Grob-like fragmentation of the central cyclobutane ring (Scheme 2c) by two possible mechanisms. Carbocation **III** (Scheme 1) could be trapped by water, followed by a retro-aldol reaction (pathway A, Scheme 2c). Alternatively, fragmentation of the Ritter intermediate (pathway B, Scheme 2c) could lead to **10**. The reaction was repeated with benzaldehyde dimethyl acetal in order to prevent formation of water on condensation with the alcohol **1**. In this case, the acetimidate **11** was isolated through trituration of the crude reaction mixture, which during purification by column chromatography hydrolyzed to a 1:1 mixture of the desired product **4a** and the fragmented ketone **10** (Scheme 2d). Isolation of the acetimidate **11** is in accord with pathway B of the proposed mechanism.

The scope of the reaction of **1** with a series of aldehydes was explored (Scheme 3a). Substituted benzaldehydes, cyclic and acyclic aliphatic aldehydes with a range of steric bulk, and unsaturated aldehydes gave the corresponding product as a single diastereomer in almost all cases. Aldehydes with longer aliphatic chains tended to give the highest yield; electron-donating/withdrawing arenes did not show a clear trend.



Scheme 3. Scope of the Prins–Ritter reaction. [a] Reaction carried out with 3,3-diethoxy-1-propyne. [b] Reaction carried out with benzonitrile solvent. [c] Reaction carried out in dichloromethane solvent.[22] Bz = benzoyl.

Prins cyclisations of the maleimides **2** and **3** were also investigated under the optimized reaction conditions. Although a 95% yield was achieved for the reaction of **2**

with dihydrocinnammaldehyde to give **5a**, the analogous reaction with benzaldehyde gave **5b** in only 43% yield. Reactions with **3** gave **6a** and **6b** in significantly lower yields (42% and 27%, respectively). Use of ketone electrophiles (acetone and cyclohexanone) gave no reaction.

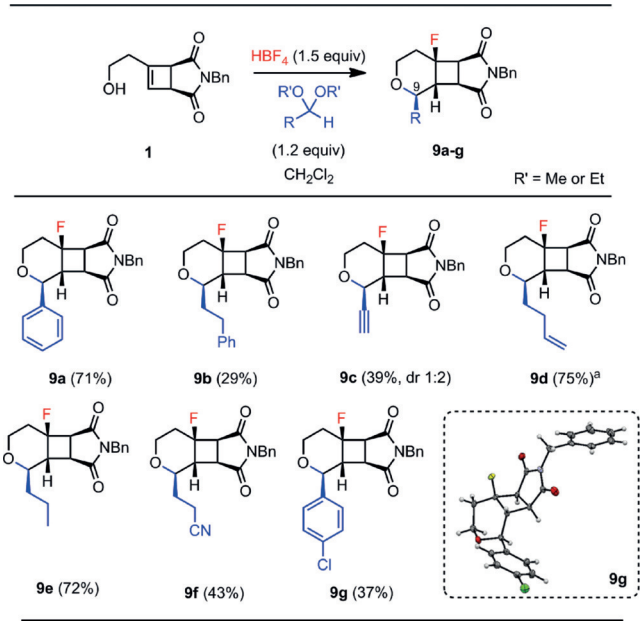
Other nitrile-based solvents could also be incorporated, for example, **1** was reacted with benzaldehyde in benzonitrile, giving tricyclic amide **7** as a single diastereomer (by NMR analysis). The structure was confirmed by X-ray crystallography (Scheme 3a). Use of five equivalents of acetonitrile in dichloromethane gave the eliminated product **8**. Alkene **8** can also be formed by conducting the reaction in dichloromethane.

As imide functionality is implicated in the formation of **10**, **1** was reduced with $LiAlH_4$ to amine **12** (Scheme 3b). Prins cyclisation of cyclobutene alcohol **12** with benzaldehyde gave the anticipated tricyclic product **13** in 78% yield, with no ketonic side product detected, also demonstrating the tolerance of the reaction to free amines.

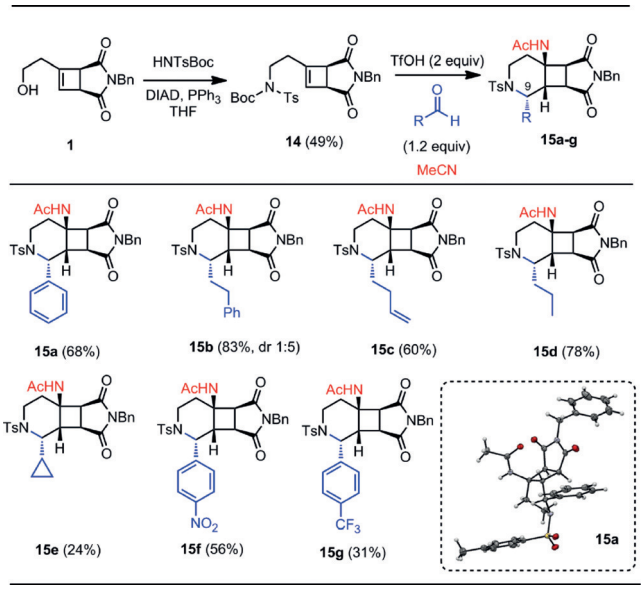
As well as the Prins–Ritter reaction, it was found that **1** reacts with a series of acetals in a process catalyzed by HBF_4 in dichloromethane to yield products with a tertiary fluoride moiety (Scheme 4). The analogous reaction with aldehydes leads to the predominant formation of ketone **10**, likely because of liberation of water. Various substituted acetals were all converted into the desired tricyclic products **9a–9g**. As with the Prins–Ritter reaction, the stereocontrol was found to be excellent in all cases (X-ray crystallography of **9g**).

As well as tricyclic tetrahydropyranyl fused rings, the corresponding piperidines were prepared by aza-Prins cyclisation (Scheme 5). Protected homoallylic amine **14** was prepared from **1** under Mitsunobu conditions. Addition of triflic acid to **14** promoted in situ deprotection of the carbamate protecting group, with subsequent addition of aldehyde yielding tricyclic products **15a–g**. X-ray crystallography confirmed the major diastereomer **15a** as having opposite stereochemistry at C9 to the oxo-Prins reaction, likely because of steric interactions caused by the nitrogen protecting group in the iminium transition state.[19] This aza-Prins sequence is notable for the stereoselective and rapid generation of tricyclic systems containing three orthogonally protected nitrogen atoms.

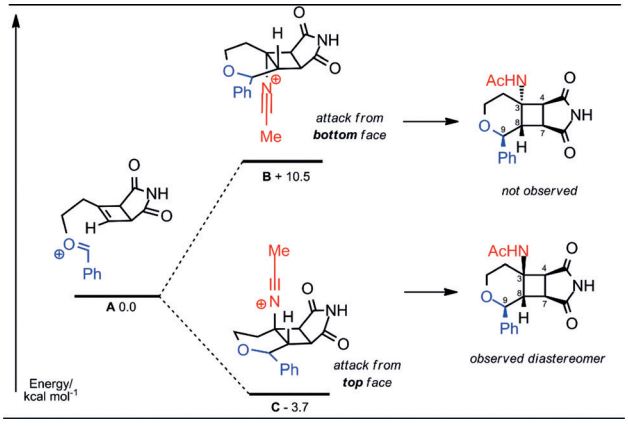
Density functional theory (DFT) calculations (B3LYP/6–31 + G(d), see the Supporting Information for details) were undertaken to explain the C3 and C8 stereochemistry (Scheme 6). The difference in stereochemistry at C9 between oxo- and aza-Prins cyclizations has been previously rationalized.[19–21] By considering the optimized geometries for the intermediates **A**, **B**, and **C**, conformational searches and



Scheme 4. Scope of the Prins reaction for the synthesis of tertiary fluorides **9a–g**. [a] Reaction carried out with 4-pentenal.[22]



Scheme 5. Synthesis of the homoallylic amine **14** and scope of the aza-Prins–Ritter reaction to give amides **15a–g**.[22] Boc = *tert*-butoxycarbonyl, DIAD = diisopropyl azodicarboxylate, Ts = *para*-toluenesulfonyl.



Scheme 6. Calculated ground-state energies of intermediates **A**, **B**, and **C** (B3LYP/6–31 + G(d), gas-phase potential energies relative to **A**; see the Supporting Information for details).

energy minimization showed that the lowest-energy conformation of **A** required the oxocarbenium ion to be positioned on the opposite face to the maleimide, thus avoiding steric clash (Scheme 6).

Facially selective cyclization accounts for the observed stereochemistry at C8. By modelling the intermediates for nucleophilic attack from both the top (**B**) and bottom (**C**) face, the stereochemistry at C3 can also be explained. Approach of the nucleophile from the bottom face (intermediate **B**) was found to be 14.2 kcal mol^{-1} higher in energy relative to the alternative mode of attack (**C**). This is strongly supportive of the *cis* relationship of C3 and C8 as observed experimentally (Scheme 6).

In conclusion, a novel application of the Prins reaction has allowed a facile synthesis of complex tricyclic sp^3-rich scaffolds in two steps. To the best of our knowledge, this is the first reported study of cyclobutenes in Prins cyclisations. Reaction times are significantly shorter (ca. 15 min) than with traditional alkene substrates. The reaction is diastereoselective, giving products with up to five contiguous stereocentres. The modular nature of this reaction allows for the incorporation of groups for further derivatization through the use of different aldehydes. Use of reaction conditions that alter the nucleophile incorporated led to the installation of both amide and fluoride quaternary centres. Finally, an aza-Prins cyclization gave tricyclic heterocyclic scaffolds containing three orthogonally protected nitrogen atoms.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cyclobutene · fluorination · photochemistry · Prins cyclization · Ritter reaction

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